Myasthenia Gravis

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Presentation lay out

- Introduction
- Definition
- Etiology
- Pathophysiology
- Role of thymus gland
- Types
- Classification
- Diagnosis
- Differential diagnosis
- Management

INTRODUCTION

- **A neurological / neuromuscular autoimmune disorder**
- **Error in the transmission of nerve impulses to muscles at the neuromuscular junction—the place where nerve cells connect with the muscles they control**
- Antibodies to the **acetylcholine receptor (AChR)**,nicotinic receptors found in the serum of 85% of patients
- **Affects 1 in 10,000 population**
- **Leads to weakness and fatigability**

Potential Risk Factors for Developing Myasthenia Gravis

Women 20-40 years old and men 50-80 years old

People who have rheumatoid arthritis or lupus

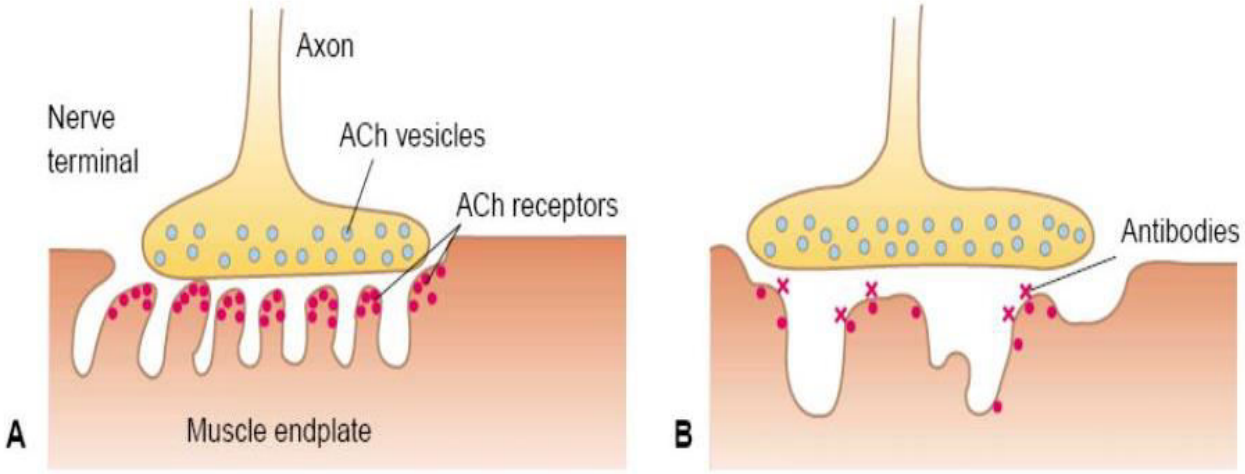
Taking certain medications for malaria, heart arrhythmia, antibiotics and psychiatric drugs

Having undergone extensive surgeries in the past

Issues with the thyroid gland

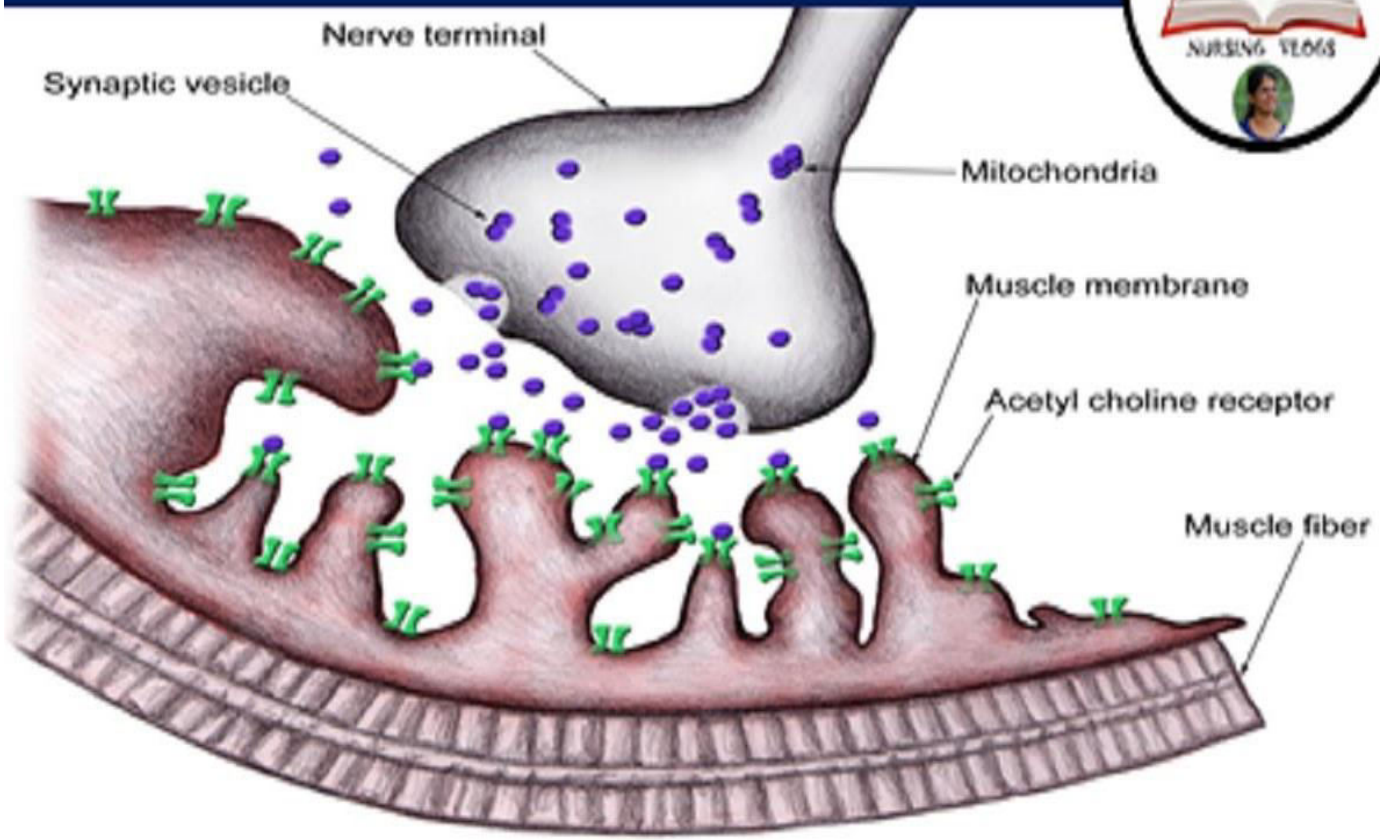
PATHOPHYSIOLOGY

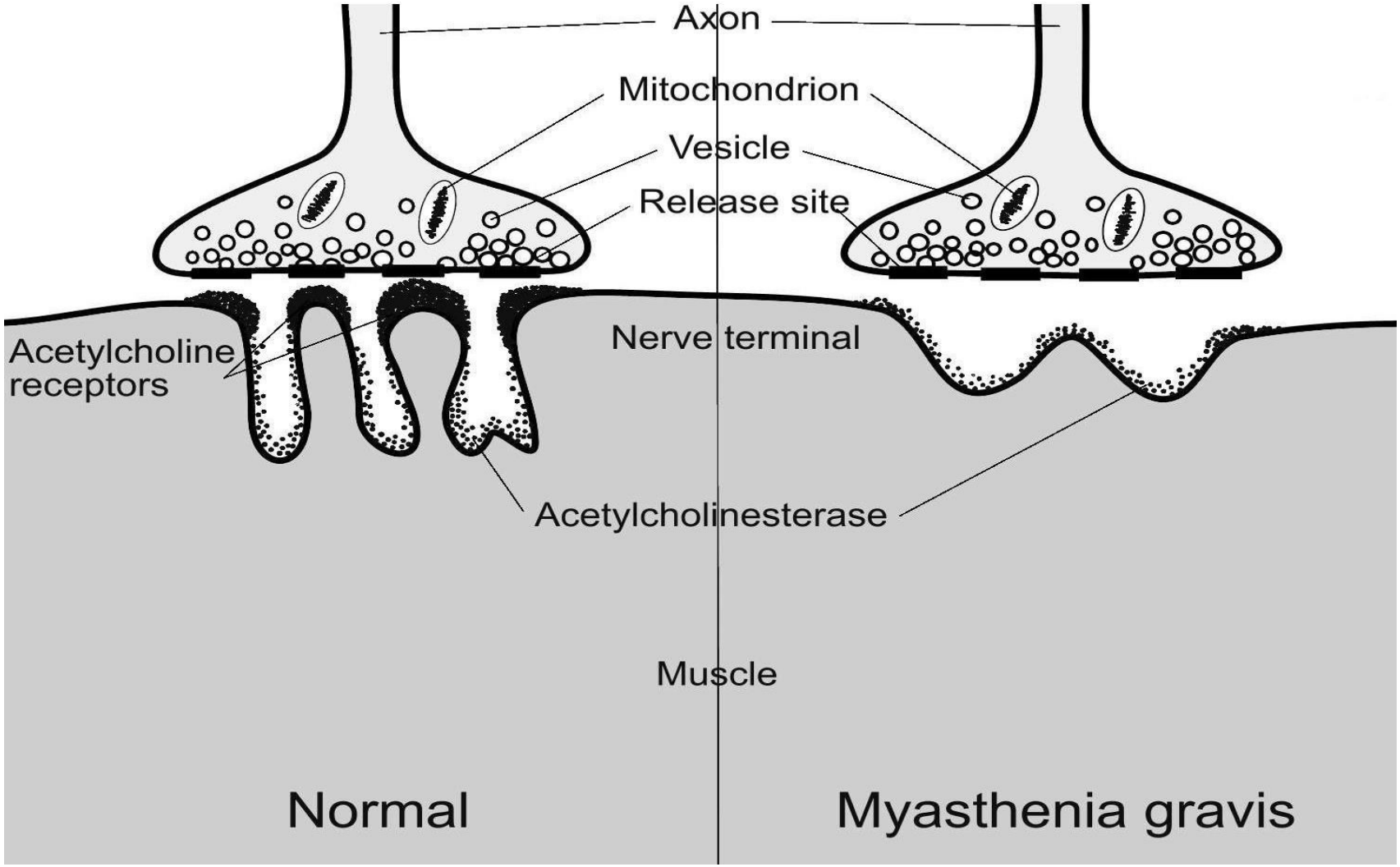
- Normally, a chemical impulse precipitates the release of acetylcholine from vesicles on the nerve terminal at the myoneural junction. The acetylcholine continuously bind to the receptor sites on the motor end plate, for muscle contraction to sustain.

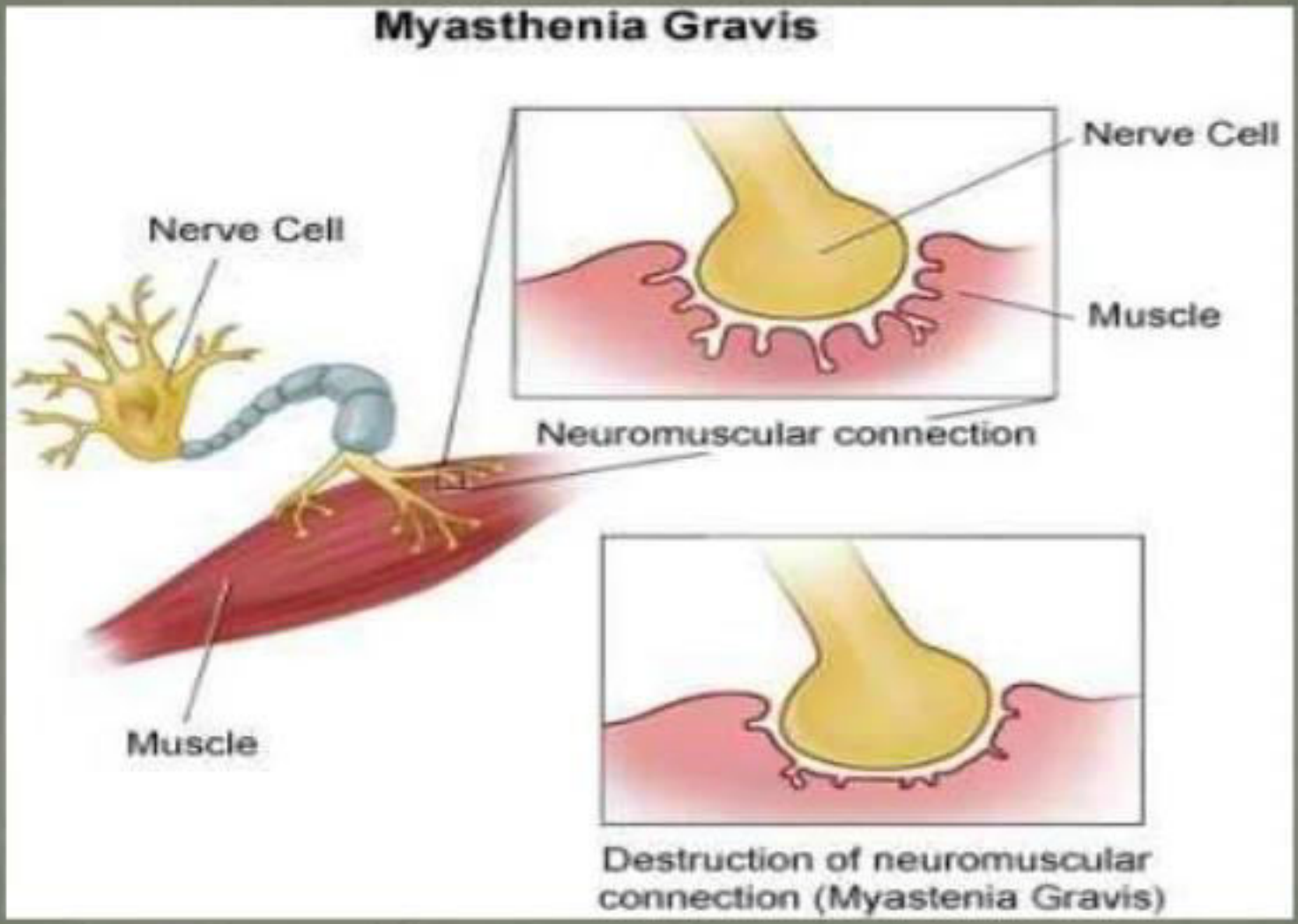


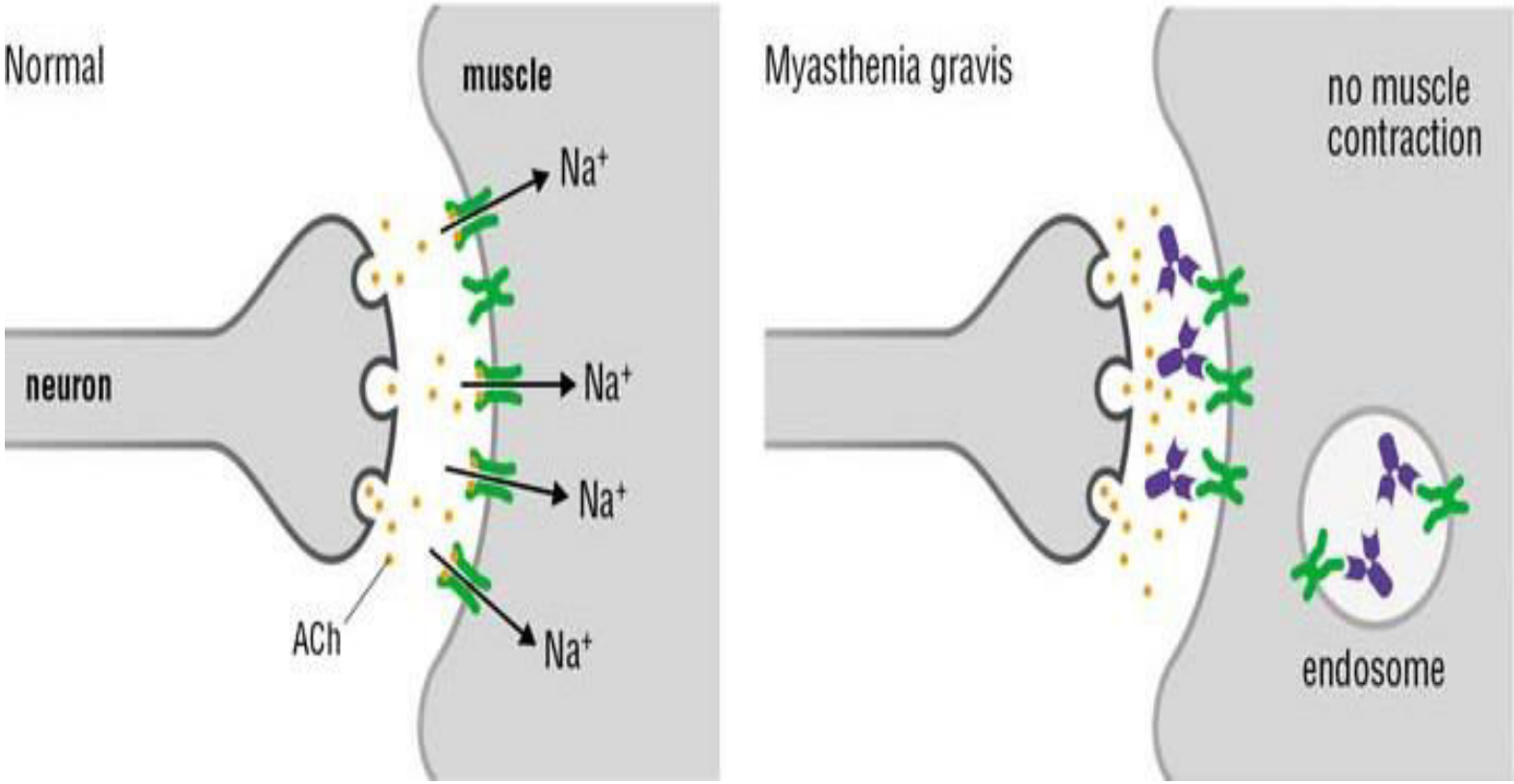
Myasthenia gravis. (A) Normal ACh receptor site. (B) ACh receptor site in myasthenia gravis.

MYASTHENIA GRAVIS



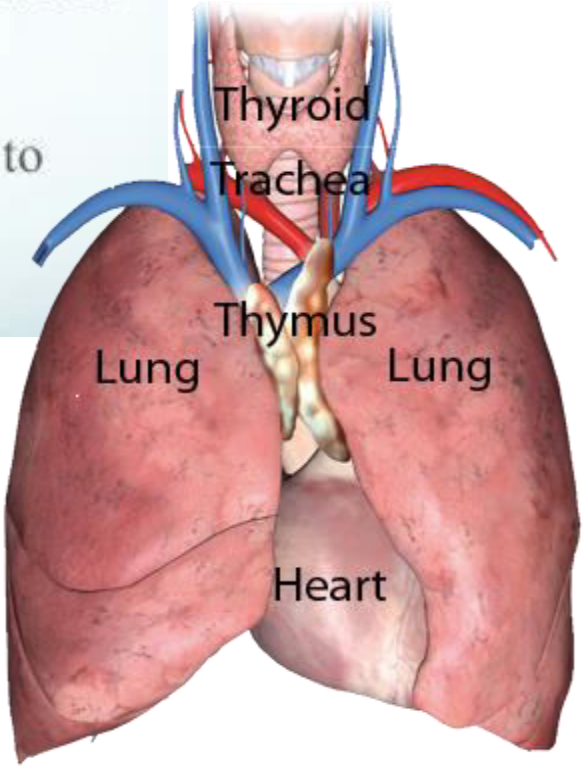

Axon
Mitochondrion
Vesicle
Release site
Acetylcholine receptors
Nerve terminal
Acetylcholinesterase
Muscle
Normal
Myasthenia gravis

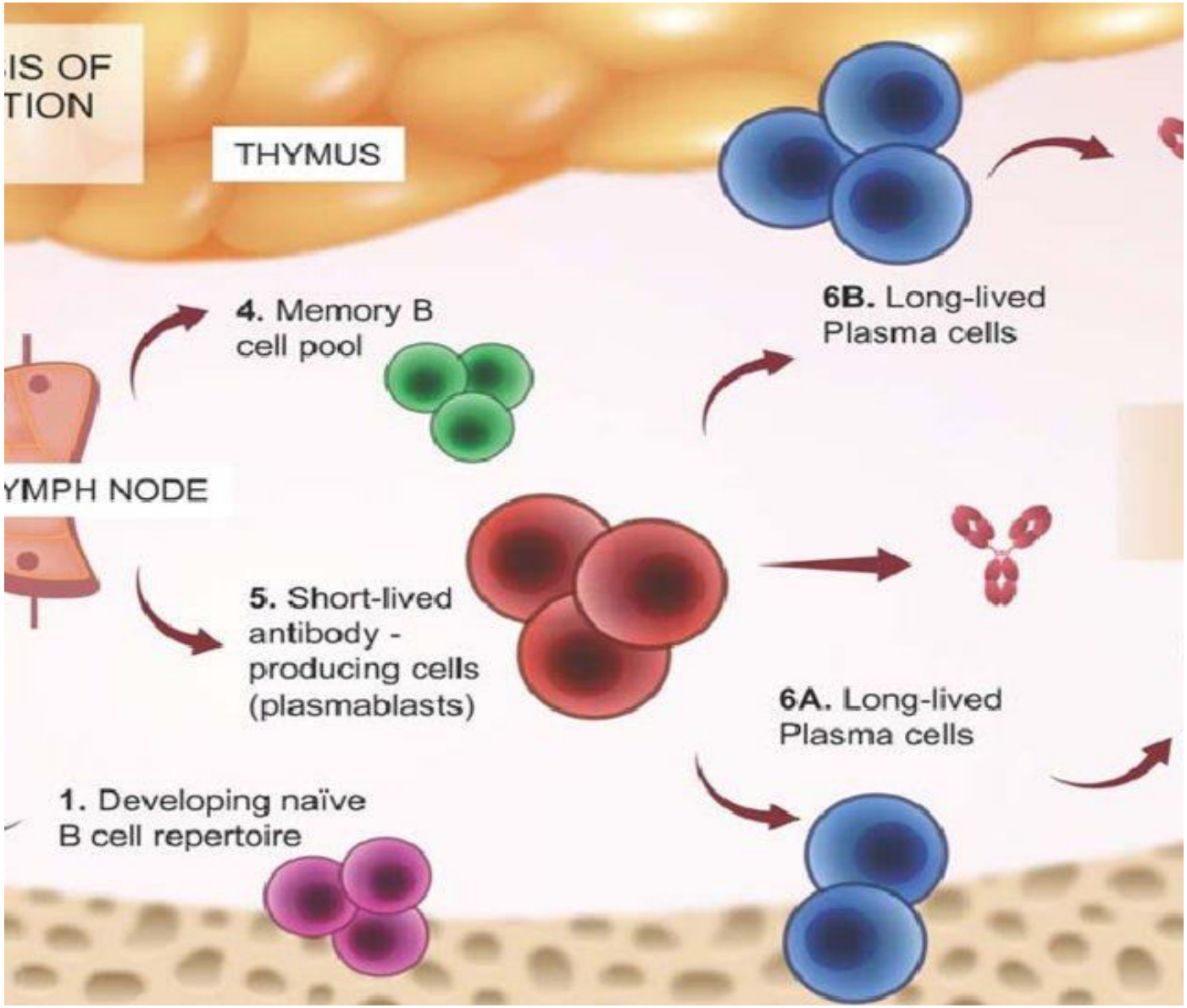

Myasthenia Gravis
Nerve Cell
Nerve Cell
Muscle
Neuromuscular connection
Muscle
Destruction of neuromuscular connection (Myastenia Gravis)


Normal
muscle
Na+
Na+
Na+
Na+
neuron
ACh
Myasthenia gravis
no muscle
contraction
endosome

ROLE OF THYMUS GLAND

- The factors that trigger the autoimmune process are not known, but the thymus gland is involved.
- The thymus lies behind the sternum and may extend down to the diaphragm or up to the neck.
- This gland plays a role in the responsiveness of T cells to foreign antigens.




IS OF
TION
THYMUS
4. Memory B
cell pool
6B. Long-lived
Plasma cells
YMPH NODE
5. Short-lived
antibody -
producing cells
(plasmablasts)
6A. Long-lived
Plasma cells
1. Developing naïve
B cell repertoire

Pathophysiology:-

- Due to etiological factors

↓

- Lymphocyte produce acetylcholine receptor antibodies that attack the post synaptic muscle membrane

↓

- Depletion of acetylcholine receptor of the neuromuscular junction

↓

Defect in the transmission of impulse from nerve to muscle cell

↓

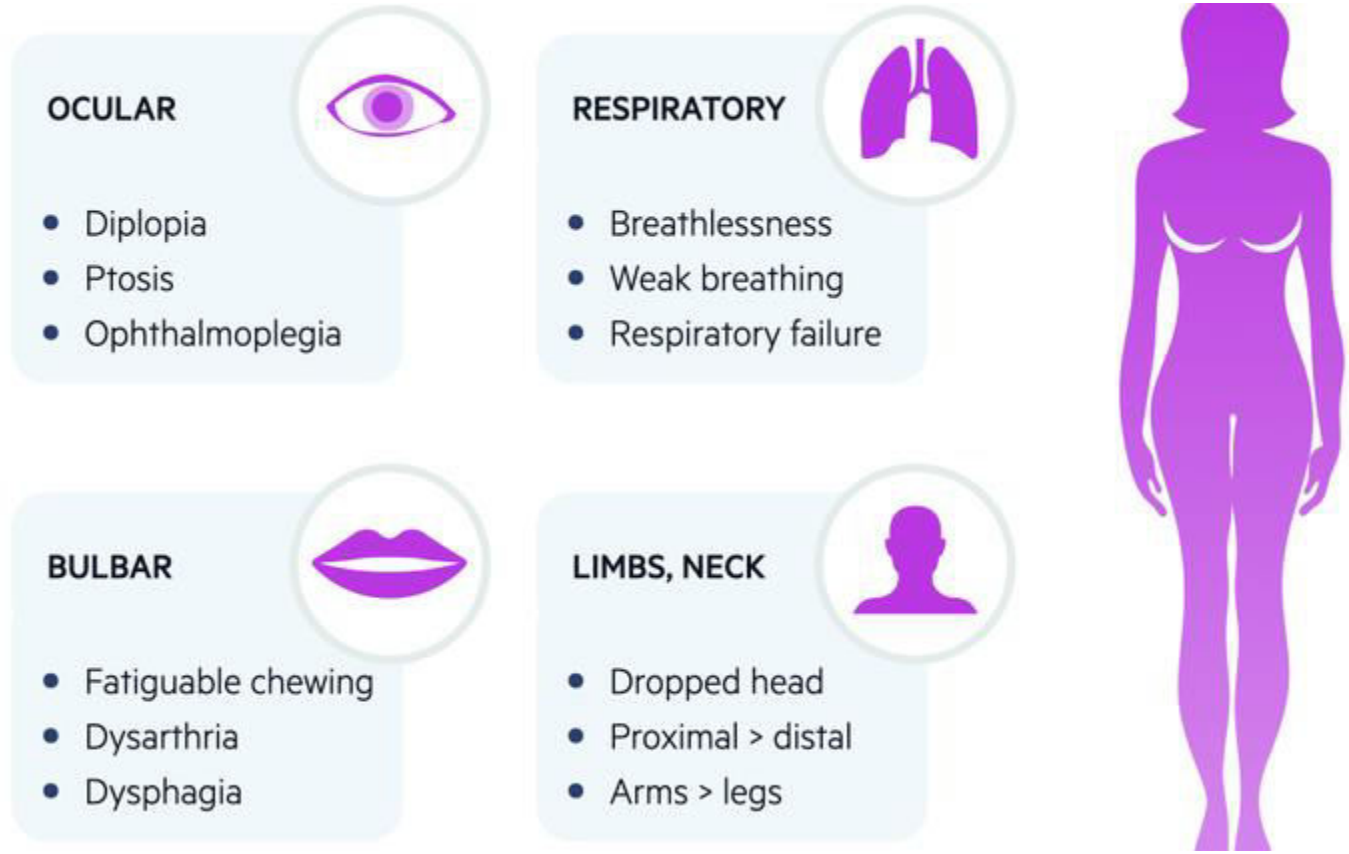
- Myasthenia gravis

Clinical Manifestations

- Muscle weakness
- Double vision (diplopia)
- weak eyelids (unilateral ptosis)
- Difficulty speaking or smiling
- Difficulty chewing and swallowing

TYPES OF MG

- **OCULAR/BULBAR/GENERALIZED**



OCULAR MYASTHENIA

- **Ocular myasthenia gravis (OMG) can mimic isolated cranial nerve palsies, gaze palsies, internuclear ophthalmoplegia, blepharospasm, and even a stroke**

Strabismus types	Number of patients (%)
Vertical deviation	6 (28.6)
Exotropia and vertical deviation	5 (23.8)
Esotropia	4 (19.0)
Esotropia and vertical deviation	3 (14.3)
Exotropia	3 (14.3)
Total	21 (100.0)

Classification

- Class I: Eye muscle weakness only
- Class II: Eye muscle weakness
  + mild weakness of other muscles
- Class III: Eye muscle weakness
  + moderate weakness of other muscles
- Class IV: Eye muscle weakness
  + severe weakness of other muscles

  OR need for nasogastric feeding
- Class V: Intubation needed to maintain airway

Diagnosis: CLINCAL, SEROLOGIC AND EMG FINDINGS

1.Clinical DX:

-Bedside: ice pack test/ Edrophonium test
- Cogan sign
- Peek sign

Imaging:

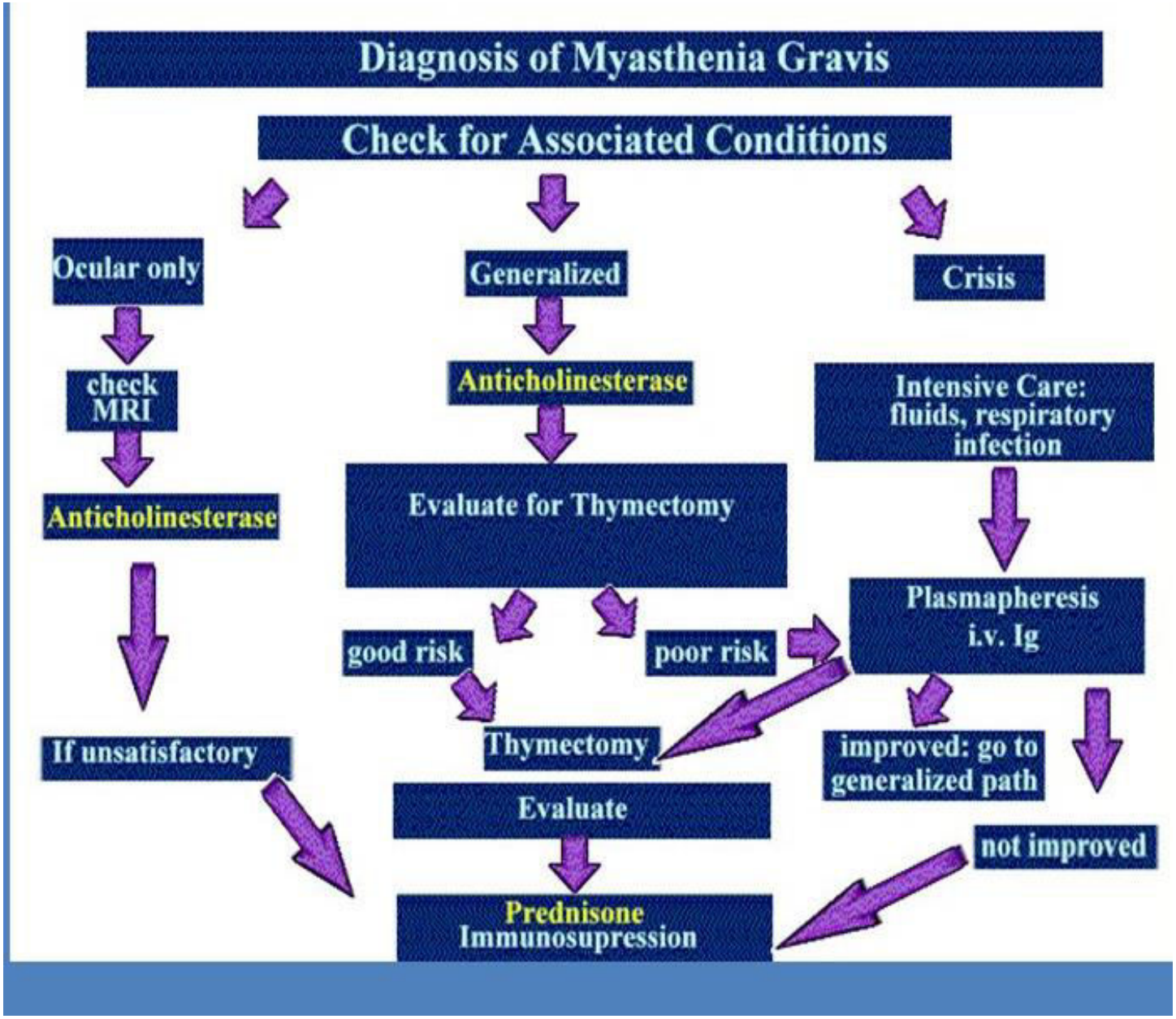
CT CHEST: Evaluate for thymoma

2.Electrophysiologic confirmation:

-Repetitive nerve stimulation
-Single fiber electromyography

3.Labs:

AchR antibodies- first step in immunologic assay
MuSK antibodies
LRP4 antibodies


Diagnosis of Myasthenia Gravis
Check for Associated Conditions
Ocular only
Generalized
Crisis
check MRI
Anticholinesterase
Intensive Care: fluids, respiratory infection
Anticholinesterase
Evaluate for Thymectomy
Plasmapheresis i.v. Ig
good risk
poor risk
If unsatisfactory
Thymectomy
improved: go to generalized path
Evaluate
not improved
Prednisone
Immunosupression

Test	Positive Result
Fatigue test	Worsening of symptoms after prolonged use
Ice test or sleep test	Improvement of ptosis after ice pack application or period of rest
Edrophonium (Tensilon or Enlon)	Improvement in symptoms within 30-60 seconds
Serologic screening	Identification of circulating AchR, MuSK or LRP4 antibodies
Electrophysiologic testing (RNS, SFEMG)	Decrease in action potential of stimulated nerves
Thyroid panel, thoracic imaging	Used to identify coexisting conditions

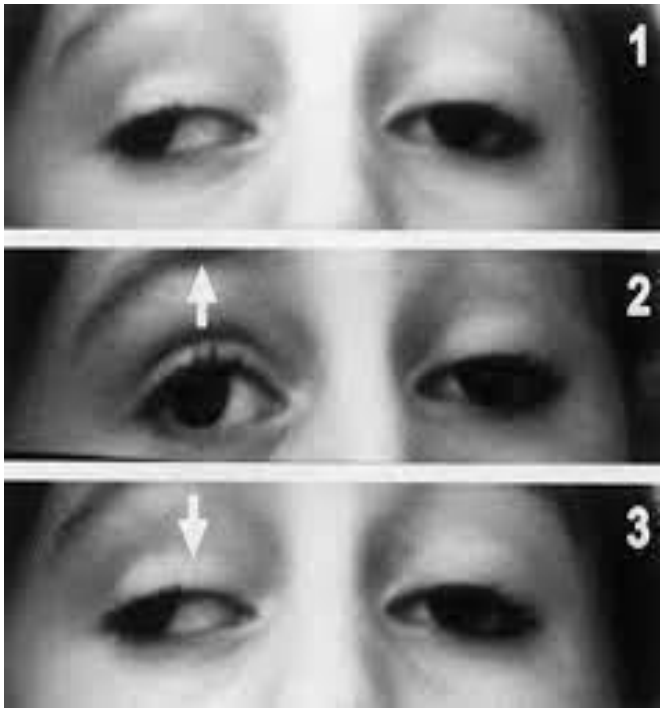
RNS = repetitive nerve stimulation; SFEMG = single-fiber electromyography

ICE PACK TEST

- Apply ice pack for 3 to 5 minutes
- Bed side test
- **Cold improves neuromuscular transmission**
- **Sensitivity of 85%**

Cogan's sign

- Ask the patient to gaze downward for 10–15 seconds and then returning to primary gaze
- Cogan's sign is present **when the affected lid briefly "twitches" upward on returning to primary gaze**

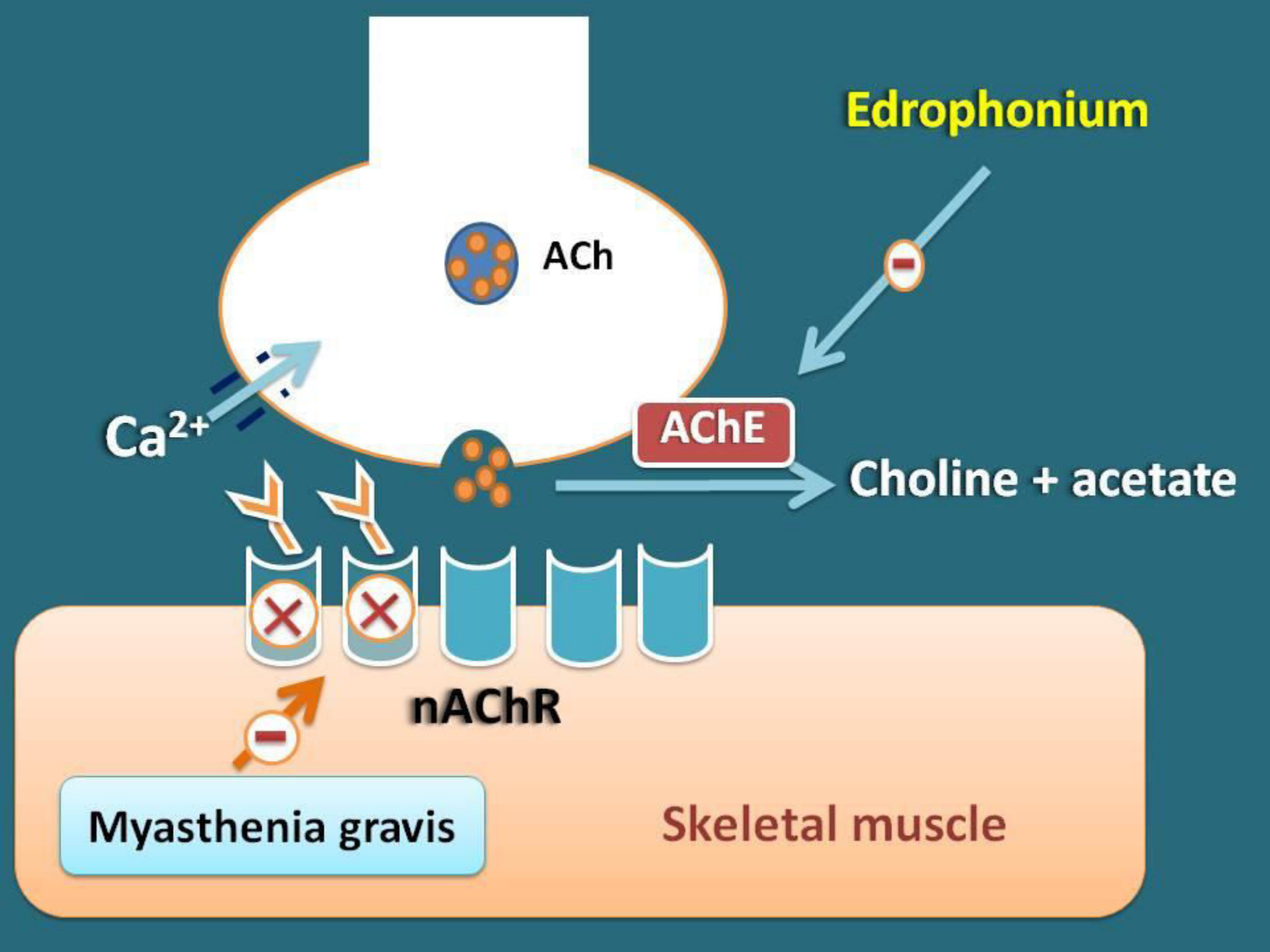


FATIGUIBILITY TEST



Tensilon Test

- Edrophonium chloride
  - Inhibits acetylcholinesterase
- Onset 30 seconds; duration 5-10 min
- NEED A CLEAR OBJECTIVE ENDPOINT
  - Works best with complete ptosis
- Compare to placebo (saline)
- Prepare atropine
- Give test dose 1-2 mg then up to 10 mg total
- SFX:
  - salivation, sweating, nausea, abdo cramping, fasciculations; hypotension & bradycardia are rare (may be as low as 0.16%)
- Sensitivity 71.5- 95%
- Specificity: not clear but can be positive in many other conditions (even ALS or normal controls)
- Not availible


Edrophonium
ACh
Ca2+
AChE
Choline + acetate
nAChR
Myasthenia gravis
Skeletal muscle

How it is given?

Initial safety check

Edrophonium

2 mg by IV

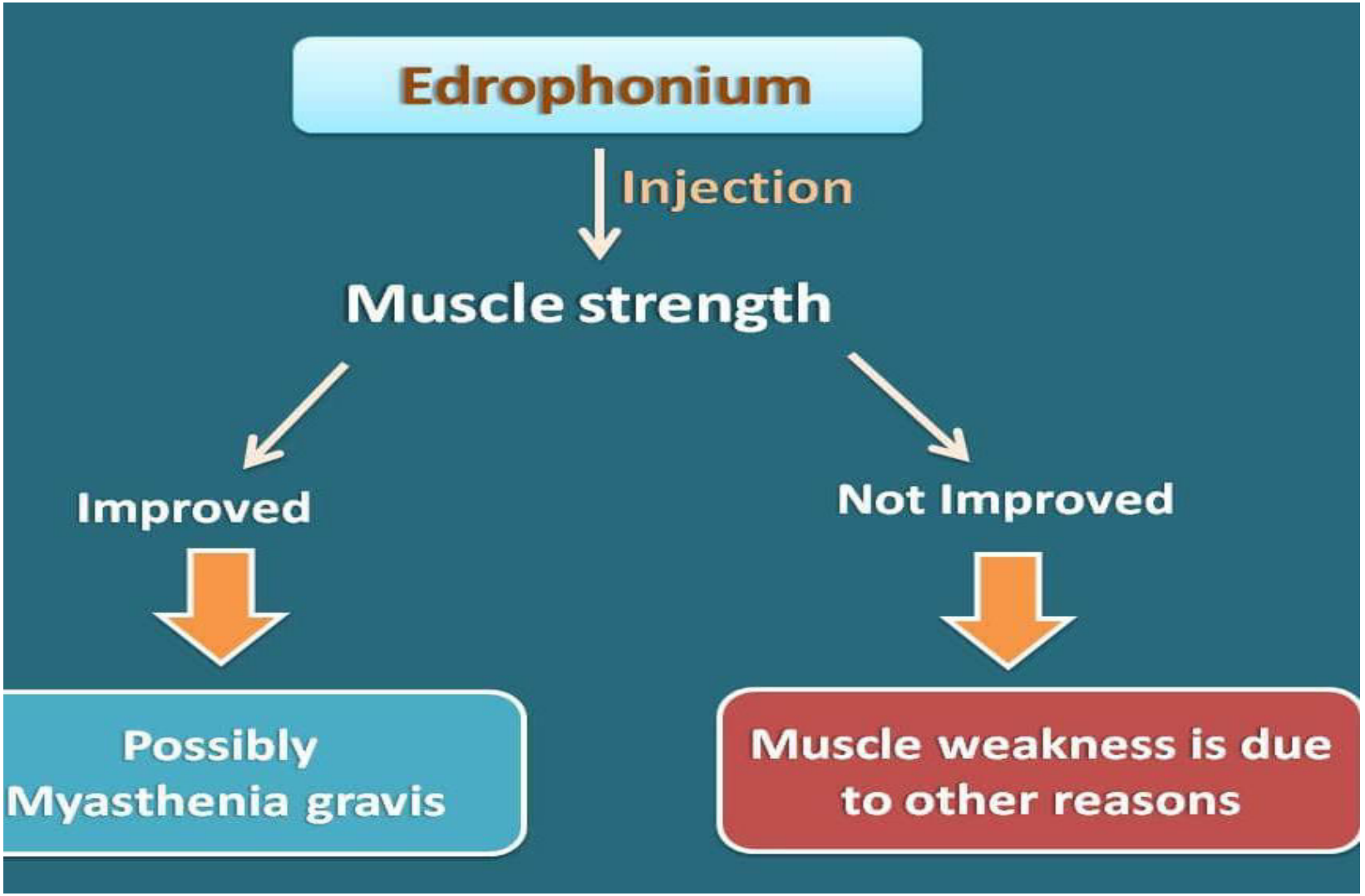
Check for any side effects

Diagnosis step

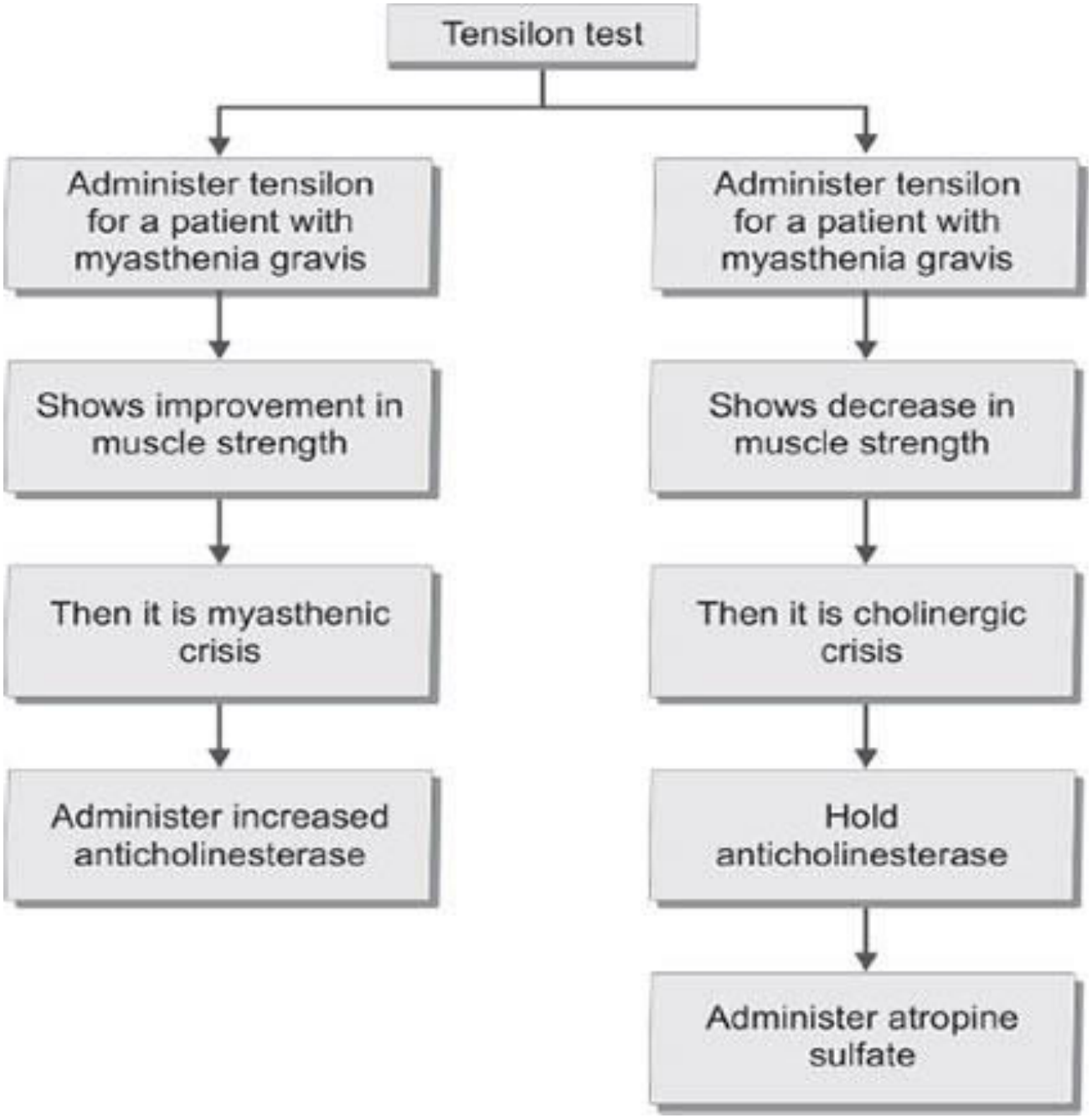
Edrophonium

8 mg by IV

Check for improvement in muscle strength


Edrophonium
Injection
Muscle strength
Improved
Not Improved
Possibly
Myasthenia gravis
Muscle weakness is due
to other reasons

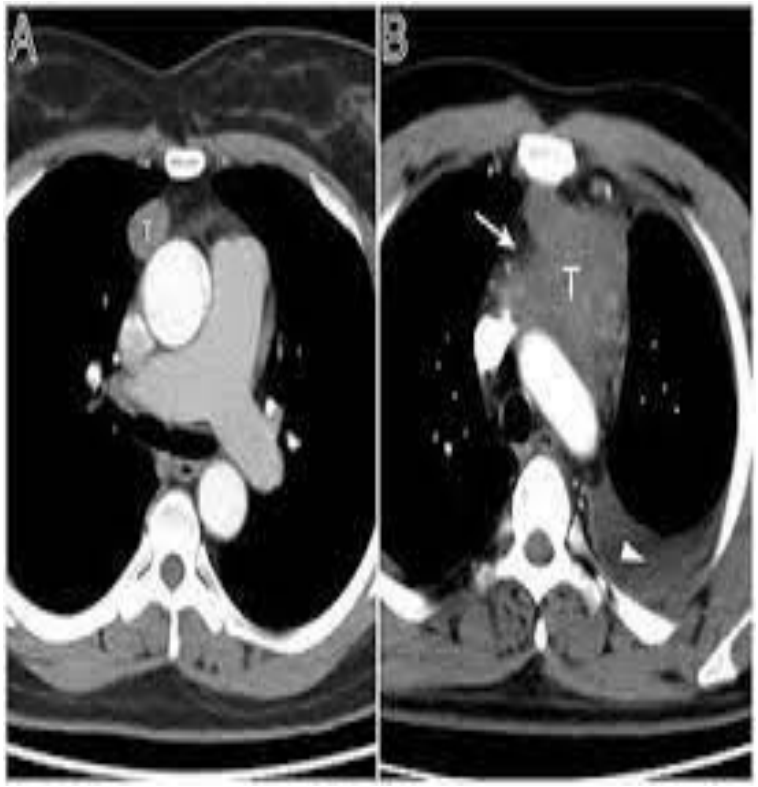
Tensilon test

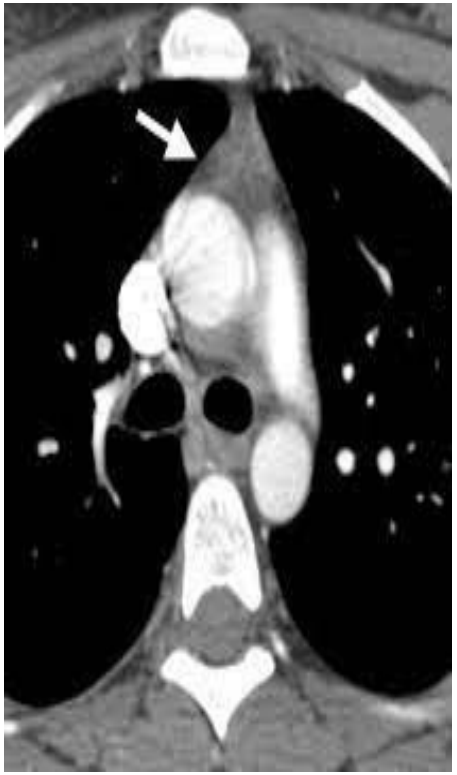

Tensilon test
Administer tensilon for a patient with myasthenia gravis
Shows improvement in muscle strength
Then it is myasthenic crisis
Administer increased anticholinesterase
Administer tensilon for a patient with myasthenia gravis
Shows decrease in muscle strength
Then it is cholinergic crisis
Hold anticholinesterase
Administer atropine sulfate

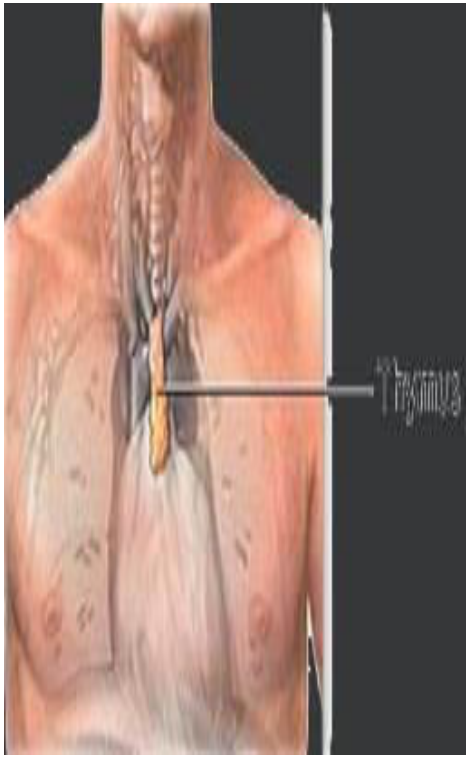
Myasthenic Crisis vs. Cholinergic Crisis

- Mysathenic Crisis
  - Serious complication where patients are unable to breathe adequately and possibly develop respiratory failure
  - Impaired swallowing and managing of secretions leading to aspiration
  - Monitory NIF, vital capacity, tidal volume
- Cholinergic Crisis
  - Due to and excess of acetylcholine at the NMJ as seen in organophosphate poisoning
  - Fasiculations, sweating, myosis, abdominal pain, bradycardia
  - Flaccid paralysis and respiratory failure
- Differentiate with edrophonium test

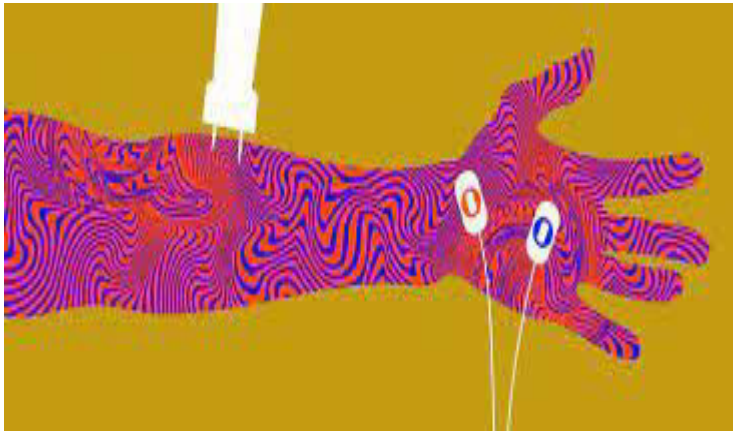
THYMOMA RADIOLOGY

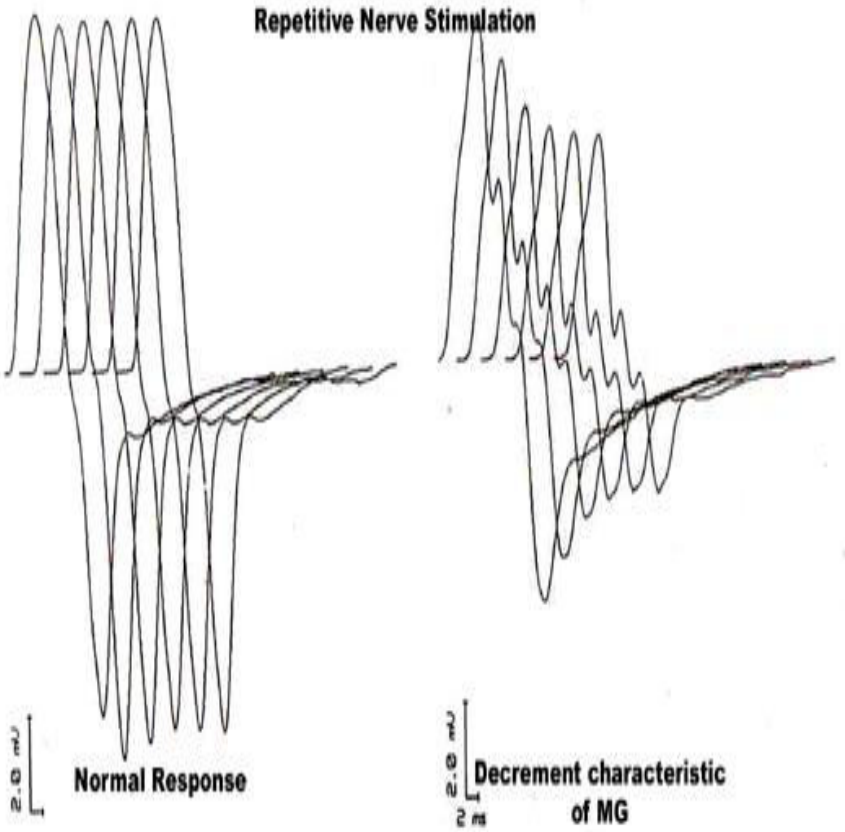




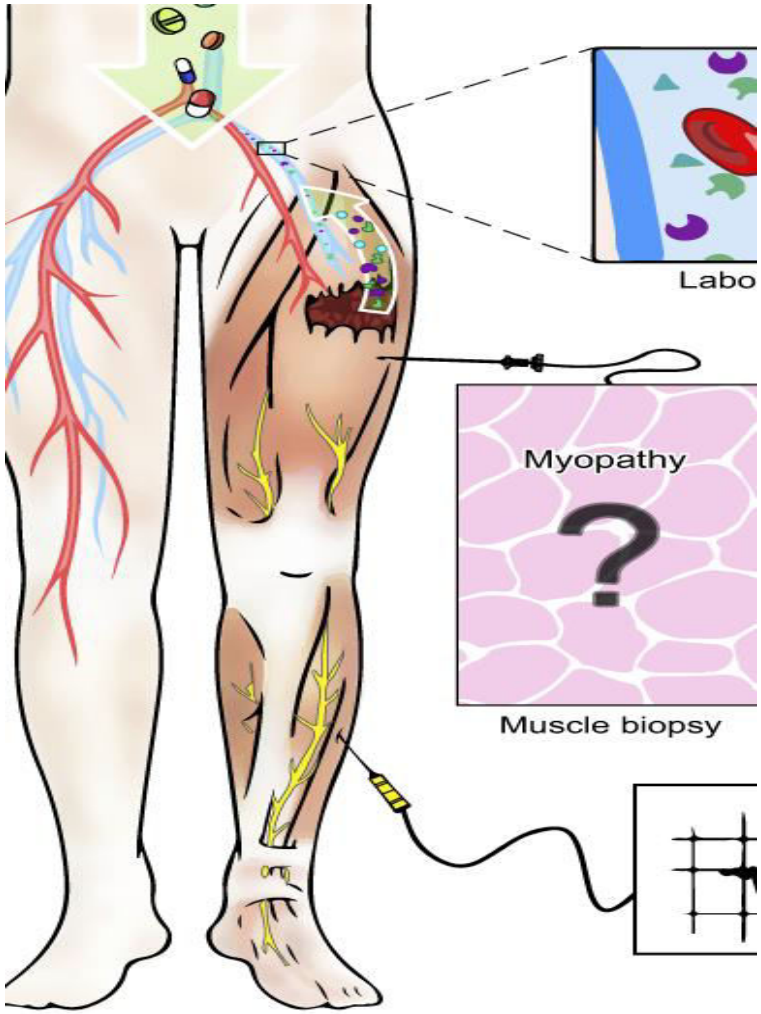


ELEECTROMYOGRAPHY
EMG Studies





MUSCLE BIOPSY



DIFFERENTIAL DIAGNOSIS

Thyroid opthalmopathy
Kearns-Sayre syndrome
Myotonic dystrophy
Brain stem/ Cranial nerve pathology
Generalized fatigue
ALS
Lambert Eaton myasthenia syndrome
Miller Fischer and PCB variants of GBS
Botulism
Penicillamine induced myastheniay

Lambert Eaton myasthenic syndrome:

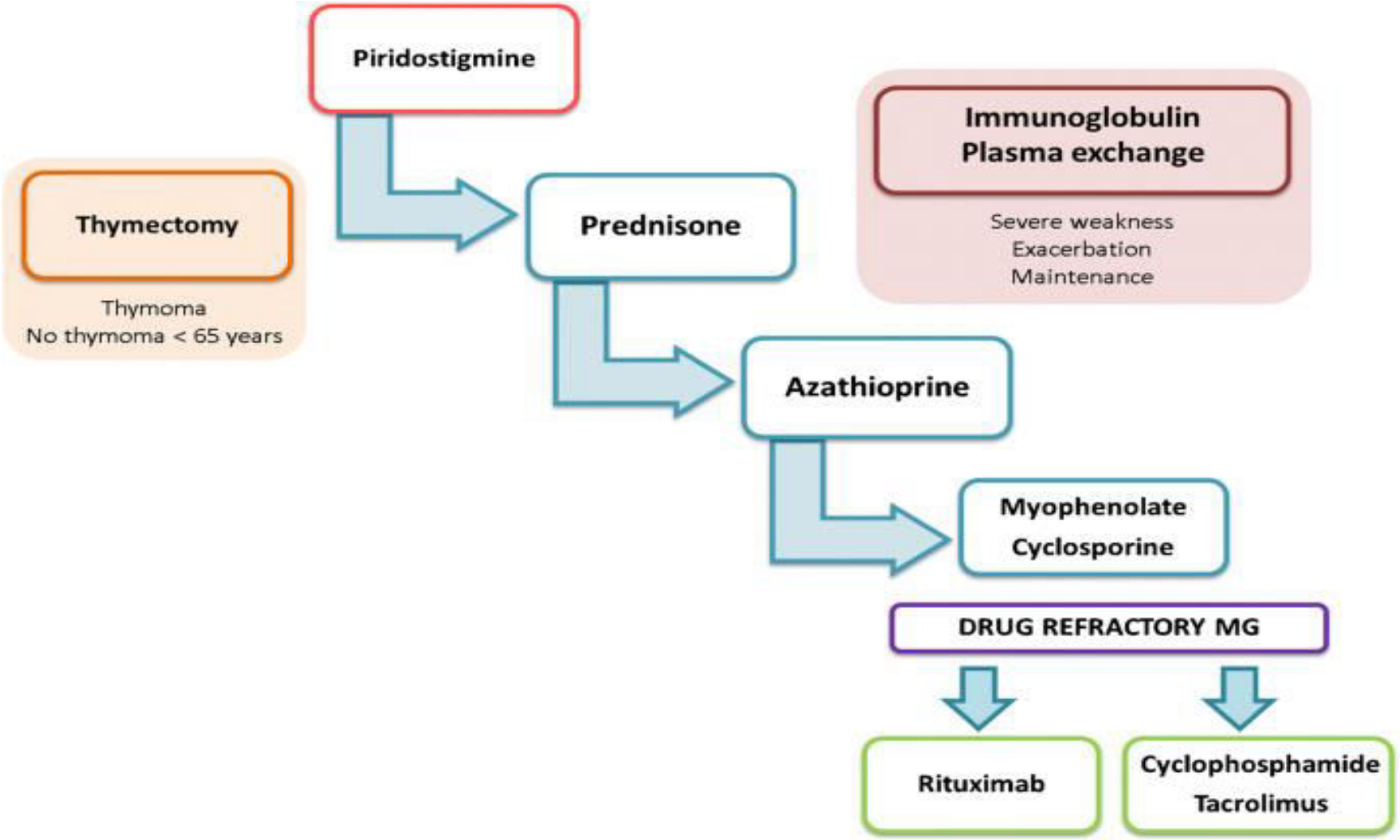
- Rare autoimmune disorder
- The immune system attacks channels that regulate calcium levels in the blood
- This causes insufficient acetylcholine to be released, leading to muscle weakness, fatigue, and other symptoms

Myasthenia gravis	Lambert Eaton syndrome
Antibody against AchR antibody	Antibody against voltage gated calcium channel
Associated with Thymic tumor	Associated with Small cell lung cancer
Weakness worsen on prolonged exercise	Weakness improves on prolonged exercise
Normal Deep tendon reflex	Decreased or absent deep tendon reflex
Autonomic dysfunction is absent	Autonomic dysfunction is present
On repeated nerve stimulation, there is decremental response	On repeated nerve stimulation, there is incremental response

Management plan

- Drug therapy
- Immunomodulation
- Surgical therapy
- Supportive therapy
- Life style modification

MANAGEMENT


Piridostigmine
Thymectomy
Thymoma
No thymoma < 65 years
Prednisone
Immunoglobulin
Plasma exchange
Severe weakness
Exacerbation
Maintenance
Azathioprine
Myophenolate
Cyclosporine
DRUG REFRACTORY MG
Rituximab
Cyclophosphamide
Tacrolimus

DRUGS USED IN MYASTHENIA GRAVIS

1) AChE inhibitors:

- Anticholinesterase inhibit Acetylcholinesterase (AchE), allowing the same Ach molecules to repeatedly interact with the available nicotinic receptors (NRs); frequency of Ach-NR interaction is increased.
- **Drugs:**
  1) Pyridostigmine bromide
  2) Prostigmine

2) Immunosuppressant medicines:

- They inhibit the immunity system, and limiting antibody production.
- **Drug:** Azothiaprine in addition to steroid medication (Prednisolone)

- **Pyridostigmine**
  Anticholinesterase with symptomatic relief

- **Rituximab (Rituxan) and eculizumab (Soliris)** are intravenous medications usually used for those who don't respond to other treatment

- **zilucoplan**, a peptide inhibitor of complement component 5 (C5 inhibitor), for the treatment of generalized myasthenia gravis in adult patients who are acetylcholine receptor antibody positive

Effects of cholinergic drugs

- CNS – enhance cognitive functions such as arousal, attention, & memory encoding – treatment for Alzheimer's disease & dementia
- Eye – pupil constriction – for surgery & treatment of glaucoma
- GI – smooth muscle stimulant – for post-op abdominal distention or paralytic ileus
- GU – urinary bladder stimulant – for post-op or postpartum urinary retention
- Musculoskeletal (indirect acting cholinergic drugs) – improve muscle tone & strength – for myasthenia gravis

Drugs that can Exacerbate Myasthenia Gravis

www.openmed.co.in

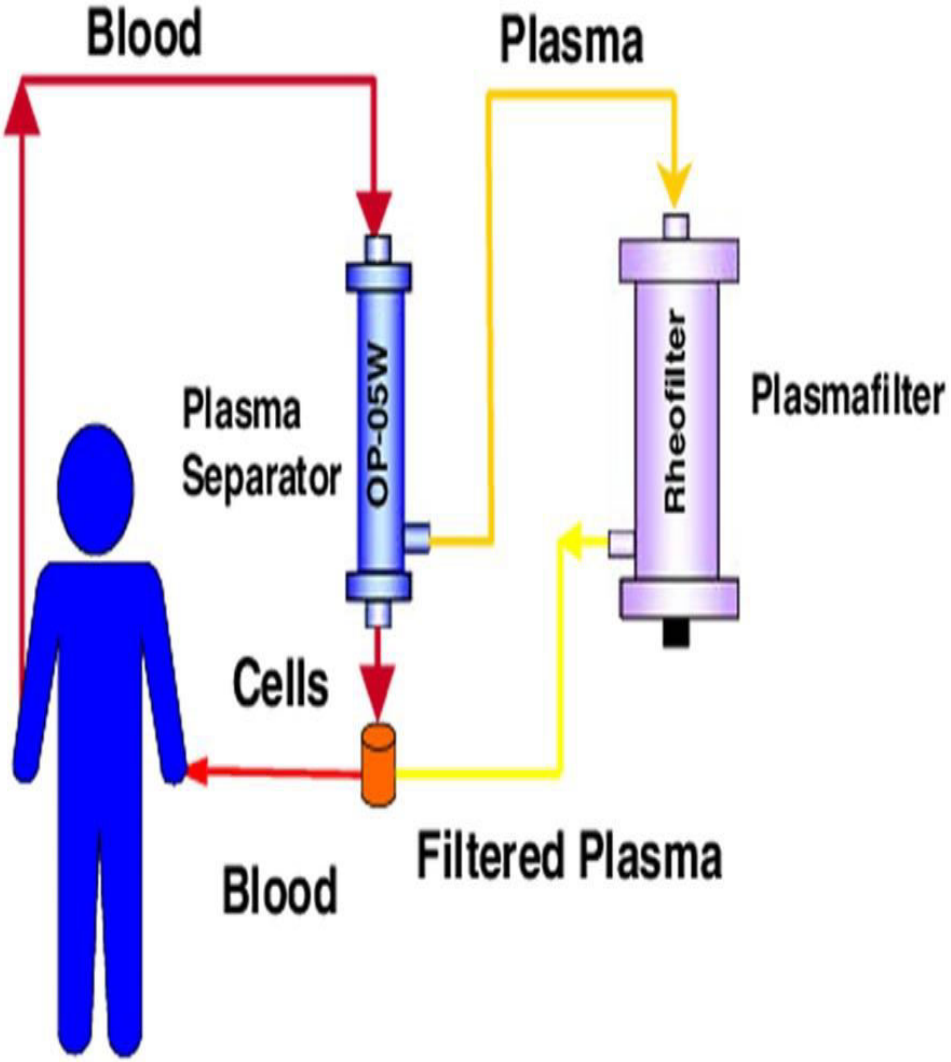
Mnemonic - *EXACERBATE*

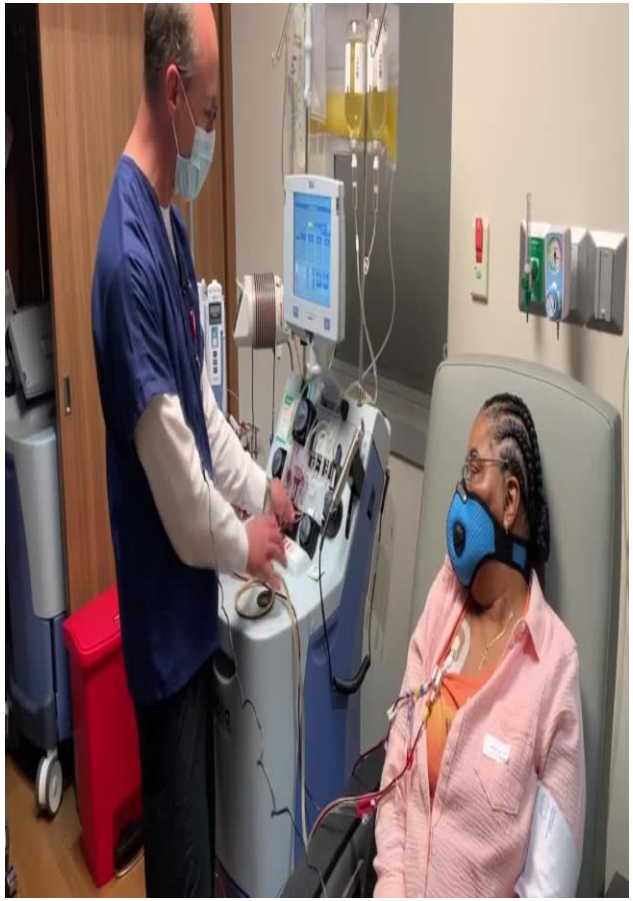
- **E**rythromycin (Macrolides)
- **X**ylocaine (Lignocaine)
- **A**minoglycosides
- **C**iproflox (Quinolones)
- **E**lectrolyte (Mg)
- **R**elaxant (Skeletal Muscle Relaxants)
- **B**otox & Beta Blocker
- **A**nti malarial (Quinine)
- **T**imolol (Eye Drops)
- **E**chothiophate (Eye Drops)

PLASMAPHERESIS

- ***A method of removing blood plasma from the body by withdrawing blood, separating it into plasma and cells, and transfusing the cells back into the bloodstream***

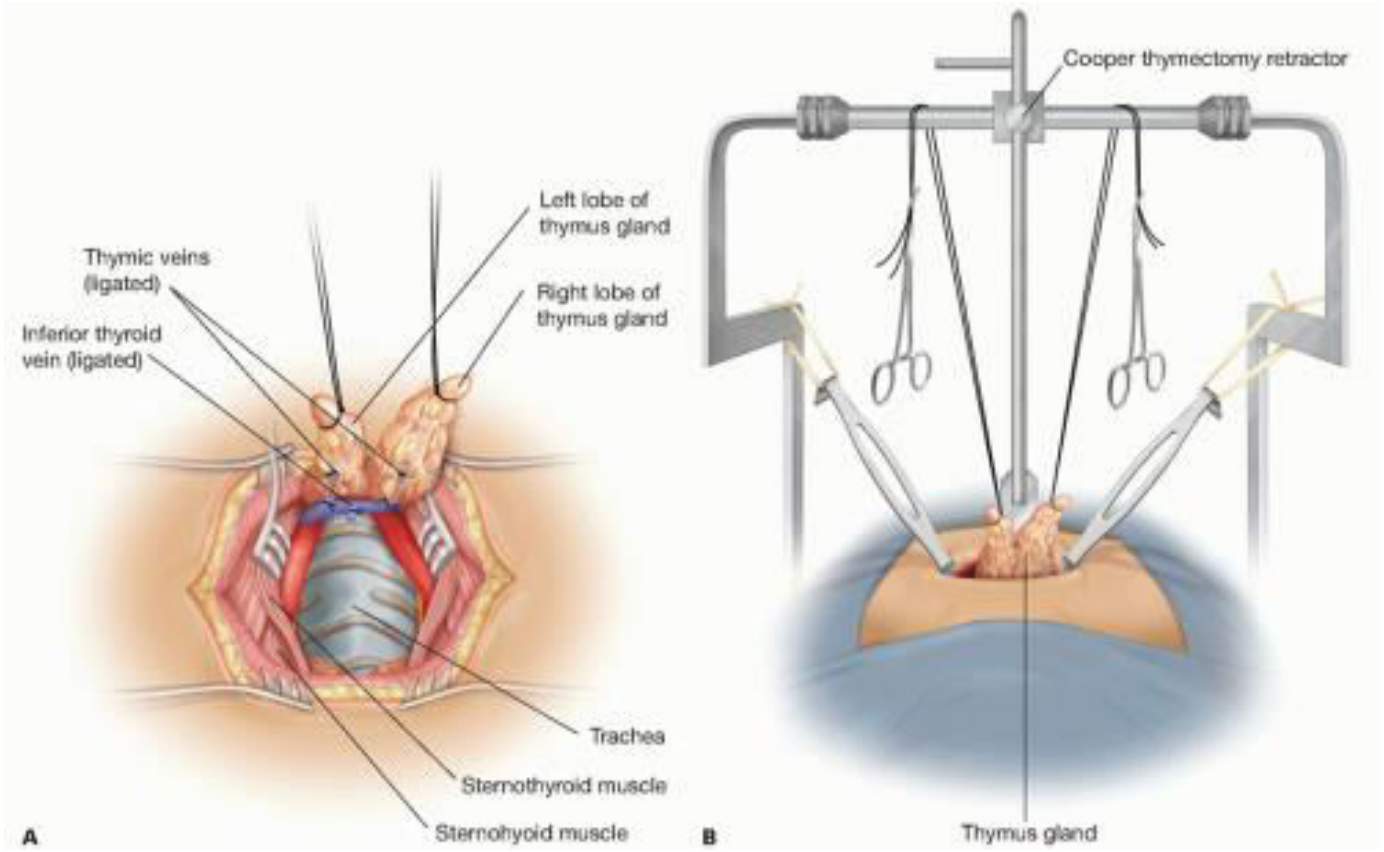
- ***It is performed especially to remove antibodies in treating autoimmune condition***


Blood
Plasma
Plasma
Separator
OP-05W
Rheofilter
Plasmafilter
Cells
Filtered Plasma
Blood

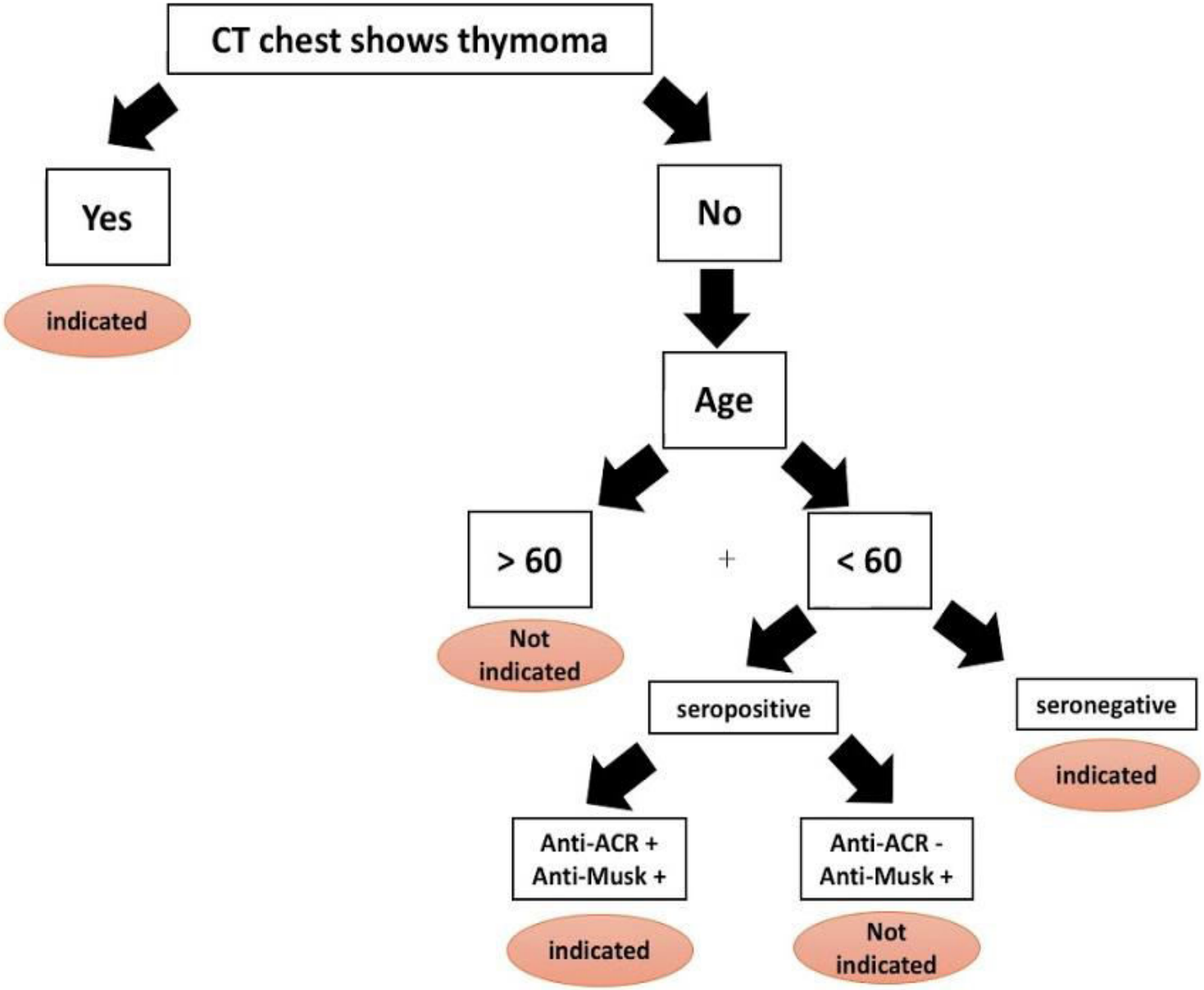


Thymectomy

- **The goal is to cause remission of the disease**
- **To allow dose reduction of harmful immunosuppressive medications**



Indications of thymectomy in Myasthenia Gravis



Life style modification

- Avoid physical exertion
- Take Plenty of Rest
- Avoid emotional stress
- Avoid exposure to extreme temperatures
- Continuous positive airway pressure therapy
- If diplopia bothers then occlusion
- Avoid medications such as muscle relaxants
- Avoid pneumonia/respiratory illness
- Avoid Low levels of potassium (diuretics and vomiting)


Myasthenia Gravis Diet Considerations
Aim to eat more small meals frequently rather than large meals
Make foods that are soft and easy to swallow or puree them
Tweak spices and temperature to boost appetite
Try out a liquid diet that includes shakes and smoothies
Incorporate thickening liquids to prevent them from being breathed into the lungs
verywell

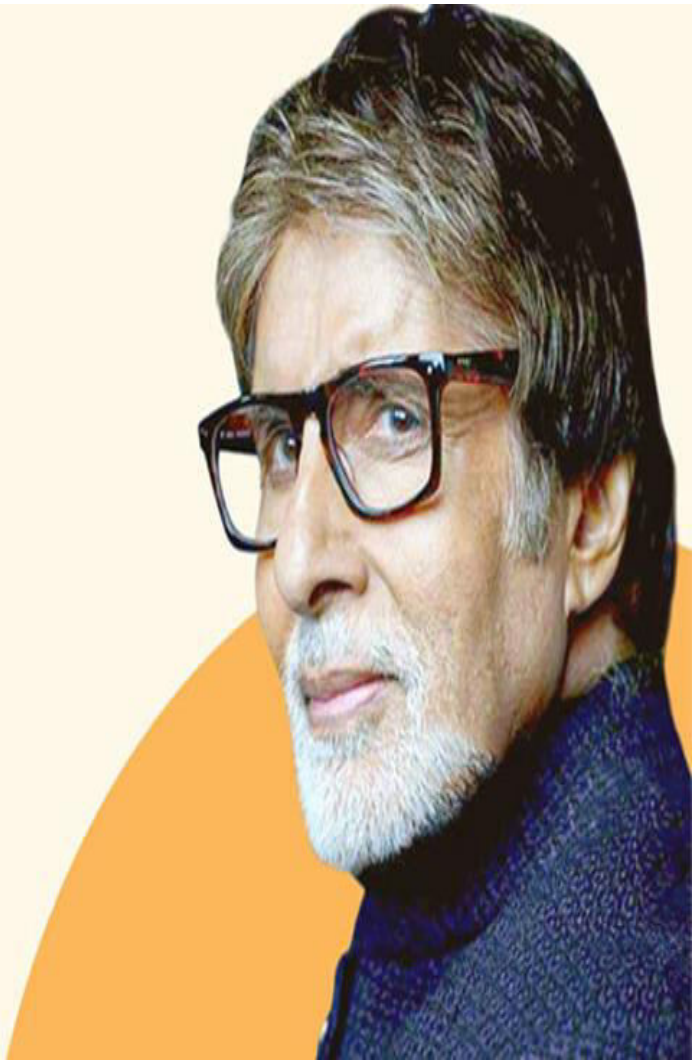
Do you know?

AMITABH BACHCHAN

is suffering from

MYASTHENIA GRAVIS

for the past 30 years!



June is....

Myasthenia Gravis Awareness Month

Many MG patients experience drastic changes in their physical appearance. For some, they may only experience changes in relation to symptoms of the MG (ex. dropping eyelids); however, others may experience changes as a side effect of medications and treatments for controlling the MG (ex. Prednisone leading to weight gain or 'moon face')

MIGRAINE

Prof SofiaIqbal
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Fellowship Orbit/Oculoplastics
Fellowship Refractive surgery

Presentation lay out

- *Introduction*
- *Definition*
- *Migraine triggers*
- *Phases*
- *Classification*
- *Pathophysiology*
- *Differential diagnosis*
- *Diagnosis*
- *Goals for treatment*
- *Management*
- *Summary of prevention*
- *Conclusion and References*

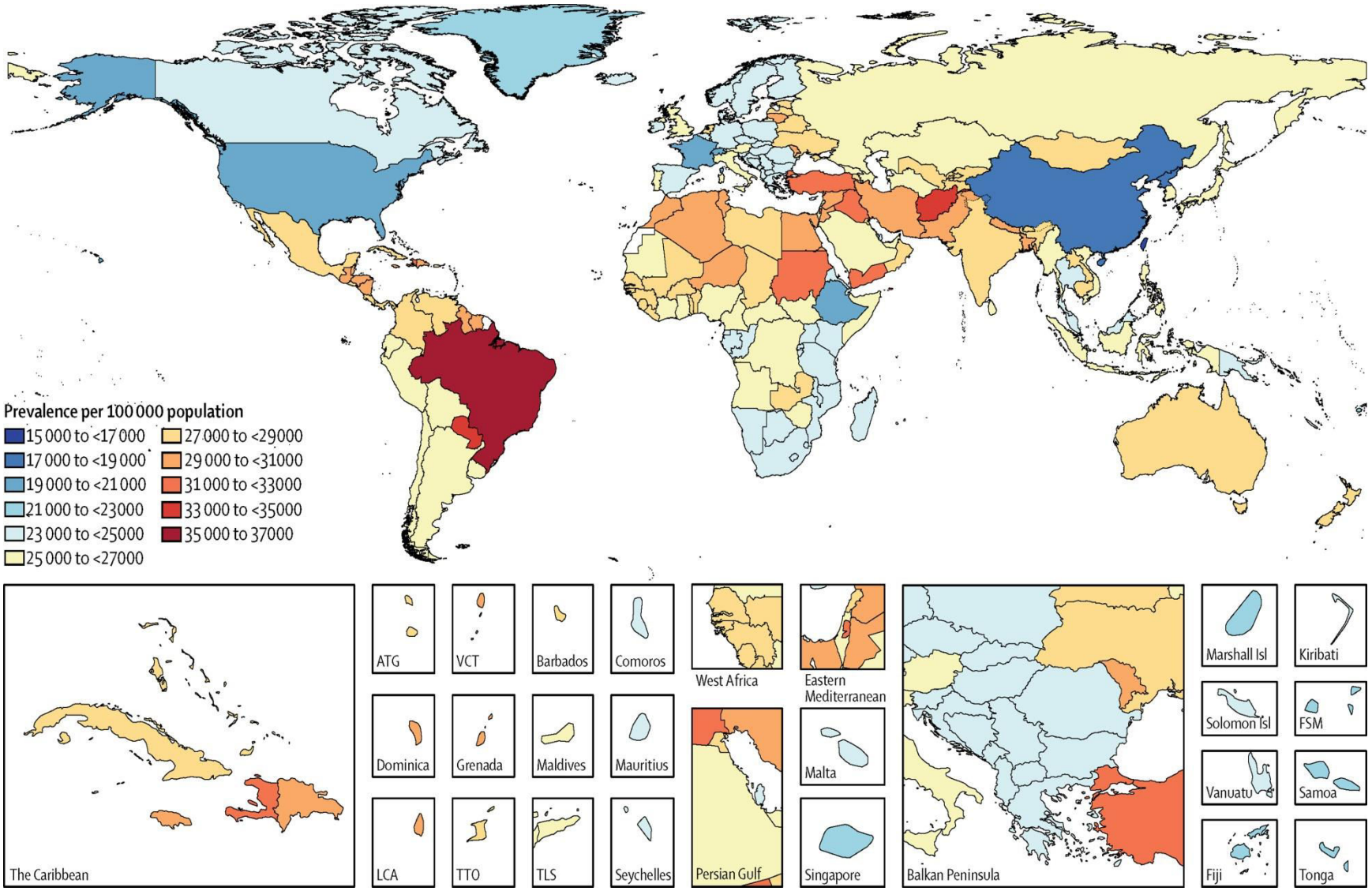
INTRODUCTION

- One of the common causes of recurrent headaches
- Constitutes 16%of primary headaches
- Migraine affects 10-20% of the general population
- It is often under diagnosed and under treated

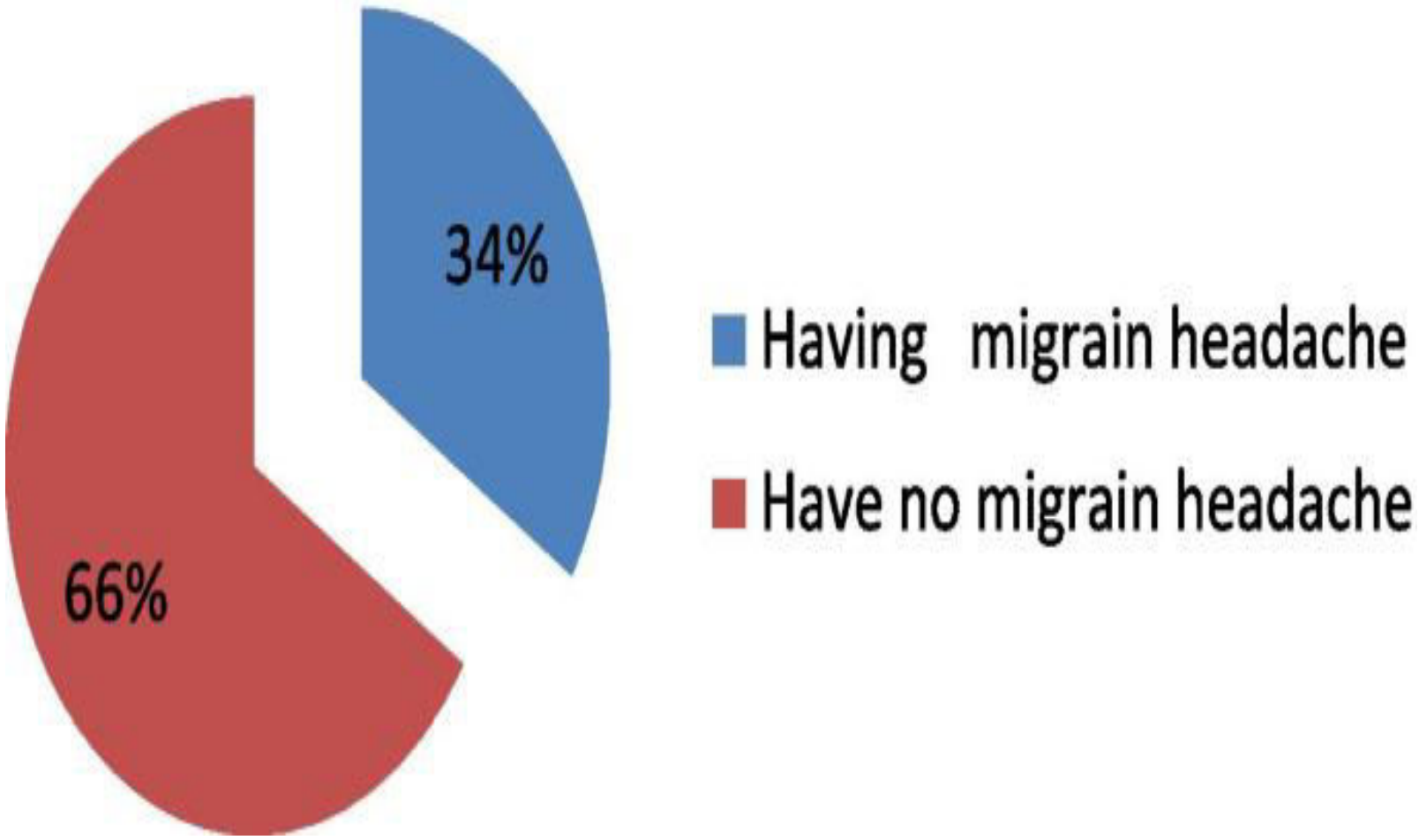
World Wide Burden

- ***It affects 18% of women and 6% of men in the US and has a worldwide prevalence of about 10%***
- ***For both men and women the prevalence rises throughout early adult life and falls after mid life***
- ***In females the rate almost triples between the age 10 and 30 years***

Global, regional and National burden



The prevalence of migrain headache



DEFINITION

- ***Originated from Greek word hemicrania meaning one side of the head***

- ***It is an episodic neurovascular phenomenon***

"Migraine is a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia nausea and vomiting"

ORIGIN OF PAIN IN THE HEAD

- Extra-cranial pain sensitive structures:
  - Sinuses
  - Eyes/orbits
  - Ears
  - Teeth
  - TMJ
  - Blood vessels
  - 5,7,9,10 cranial nerves carry pain from thes strucure
- Intra-cranial pain sensitive structures:
  - Arteries of circle of willis and proximal dural arteries,
  - Dural Venous sinuses,veins
  - Meninges
  - Dura

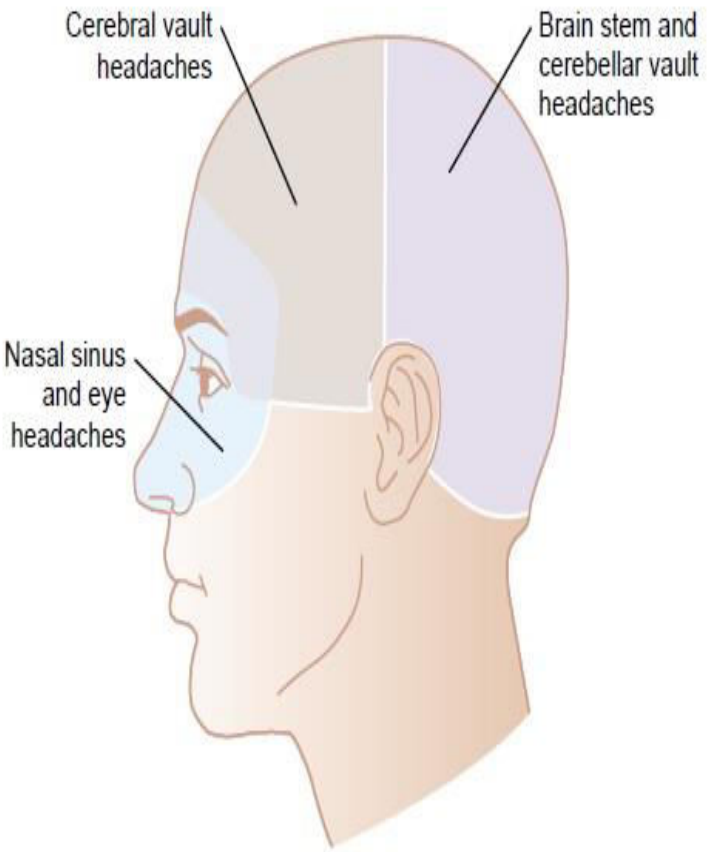


Figure 48–9

Areas of headache resulting from different causes.

Is it a migraine or type of headache?

	Migraine	Tension Headache	Sinus Headache	Cluster Headache
Location of pain	1 or both sides of head	1 or both sides of head or neck	Face, forehead, between eyes	1 side, extending from behind eye
Duration	4–72 hours	2 hours to days	Days, if untreated	30-90 minutes
Intensity	Mild, moderate or severe	Mild or moderate	Mild to severe	Severe
Treatment options	OTC medicines	Prescription from doctor	Decongestants or antibiotics	Oxygen and triptans

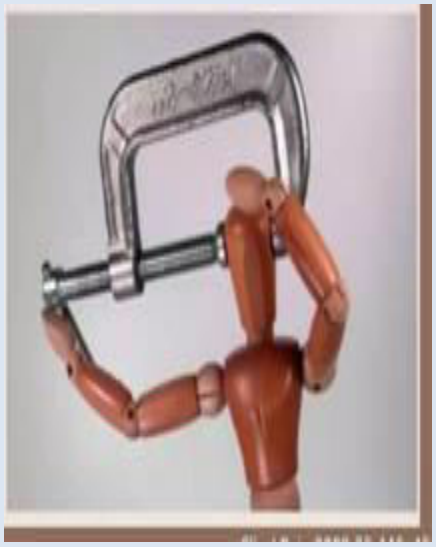
Primary Headache Types

	Migraine	Tension	Cluster
Pain Description	Throbbing, moderate to severe, worse w/exertion	Pressure, tightness, waxes and wanes	Abrupt onset, deep, continuous, excruciating, explosive
Associated Symptoms	Photo/phono-phobia, n/v, aura	None	Tearing, congestion, rhinorrhea, pallor, sweating

	Migraine	Tension	Cluster
Location	60-70% unilateral	Bilateral	Unilateral
Duration	4-72 hr	Variable	0.5-3 hr, many per day
Patient Appearance	Resting in quiet dark room; young female	Remains active or prefers to rest	Remains active, prefers hot shower, male, smoker

MIGRAINE TRIGGERS

- *Disturbed sleep pattern*
- *Hormonal changes*
- *Physical exertion*
- *Drugs (birth controls and vasodilators)*
- *Visual stimuli*
- *Auditory stimuli*
- *Olfactory stimuli*
- *Hunger*
- *Specific foods (alcohol and caffeine)*
- *Weather changes*
- *Psychological factors*



The role of foods and supplements in migraine

- **Skipped meals and fasting** were reported migraine triggers in over **56%** in a population-based study and **40% to 57%** in subspeciality clinic-based studies
- The mechanism by which fasting and skipping meals triggers headaches may be related to **alterations in serotonin and norepinephrine in brainstem pathways or the release of stress hormones such as cortisol.**

Clin J Pain 2009;25:446–452

External triggers

Dietary

- Caffeinated beverages
- Alcoholic beverages
- Aged cheeses
- Chocolate
- Coffee, tea, cola
- Chocolate
- Food allergens (Dairy products, yogurt)
- Ice cream

Chemical

- Monosodium glutamate
- Tyramine
- Nitrates
- Artificial sweetener (Aspartame)

Environmental

- Bright light/visual stimuli
- Odors/smells
- Weather changes
- Cigarette smoke

Behavioral

- Stress/tension
- Hunger/not eating
- Emotions
- Lack of sleep and Sleeping late/excess
- Fatigue/tiredness
- Exercise
- Hair wash or head bath

Minor head trauma

feels like CHOCOLATE

(causes of migraine)

Cheese ☑

OCP ☑

Caffeine ☑ the ones I do...

Alcohol ☑ ... ah shit.

Anxiety ☑

Travel ☑

Exercise ☑

Internal triggers

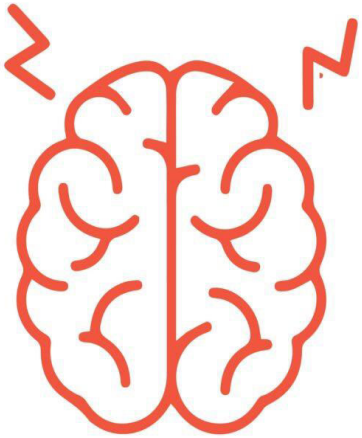
- The most common internal triggers are **sex hormones (neurosteroids and ovarian steroids).**
- The key stages of reproduction including **first menstruation, pregnancy and menopause** are associated with frequency or severity of migraine.
- Interestingly only attacks of migraine without aura occur during the perimenstrual time period and attacks of migraine with aura happen equally during the menstrual cycle.

- **P** Pulsatile
- **O** hOurs (duration of 4-72 hours)
- **U** Unilateral
- **N** Nauseating
- **D** Disabling

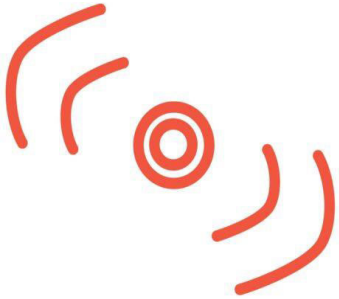
knowmedge
MEDICAL MNEMONICS

Mnemonic: "POUNDing Headache"

COMMON MIGRAINE SYMPTOMS

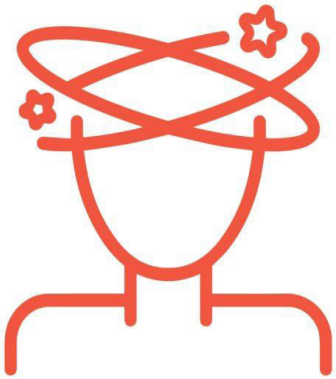


PAIN ON ONE OR BOTH SIDES OF HEAD



THROBBING OR PULSING

SENSITIVITY TO LIGHT, SOUND, OR MOVEMENT

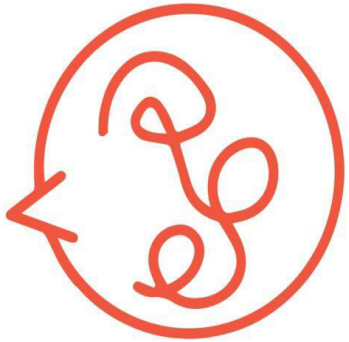


NAUSEA AND VOMITING

TEMPORARY LOSS OF VISION

ISOLATED WEAKNESS OR NUMBNESS

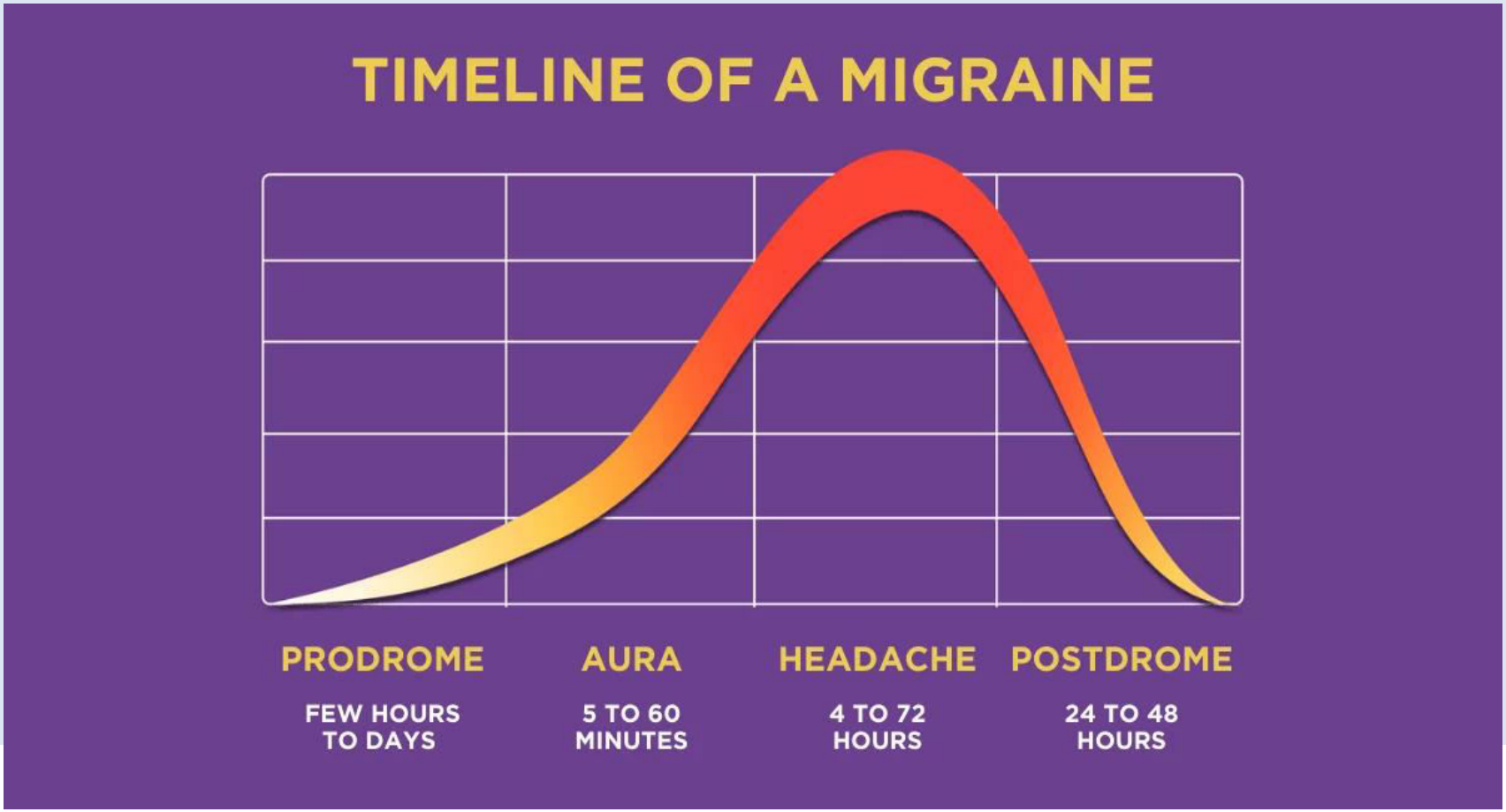
"PINS AND NEEDLES" IN EXTREMITIES



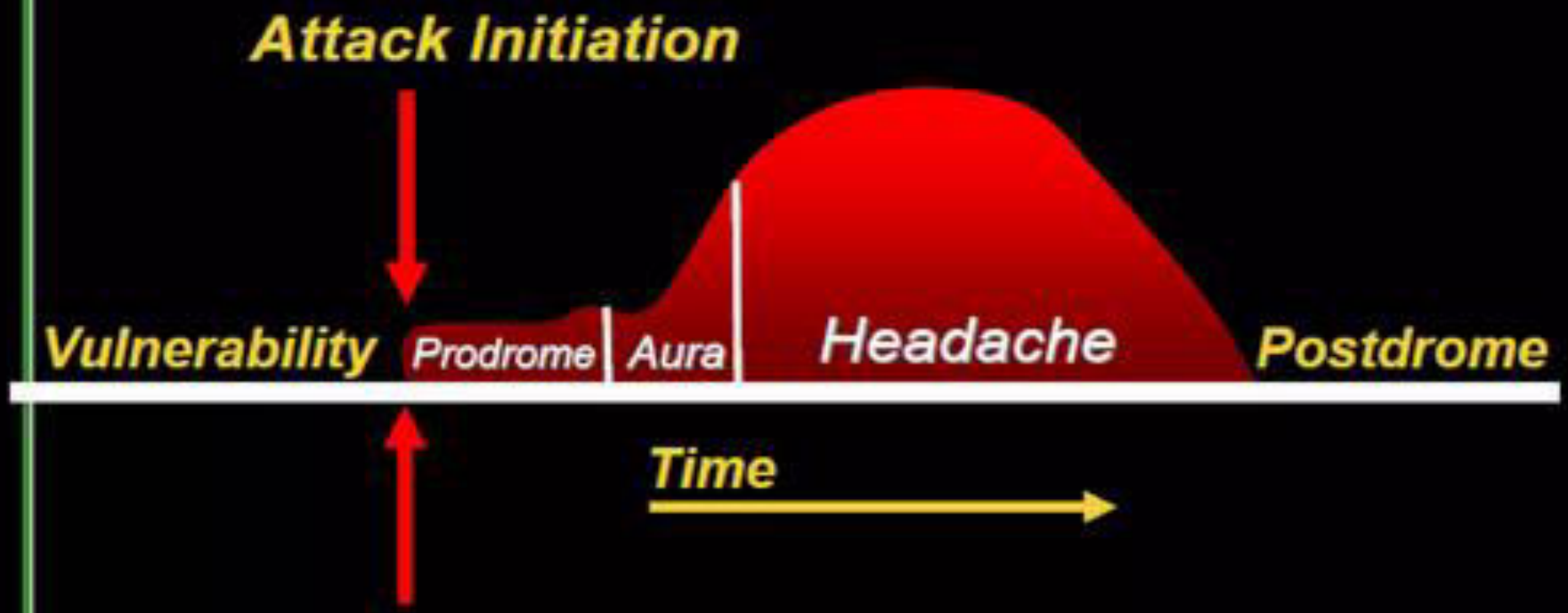
TEMPORARY TROUBLE WITH SPEECH

PHASES

- **Prodrome, Aura, Headache and Postdrome**



CLINICAL PHASES OF A MIGRAINE ATTACK



Blau JN. *Lancet*. 1992

PRODROME

- ***Vague premonitory symptoms that begin from 12 to 36 hours before aura and headache***

Symptoms

- Yawning
- Excitation
- Depression
- Lethargy
- Craving or distaste for various foods

AURA

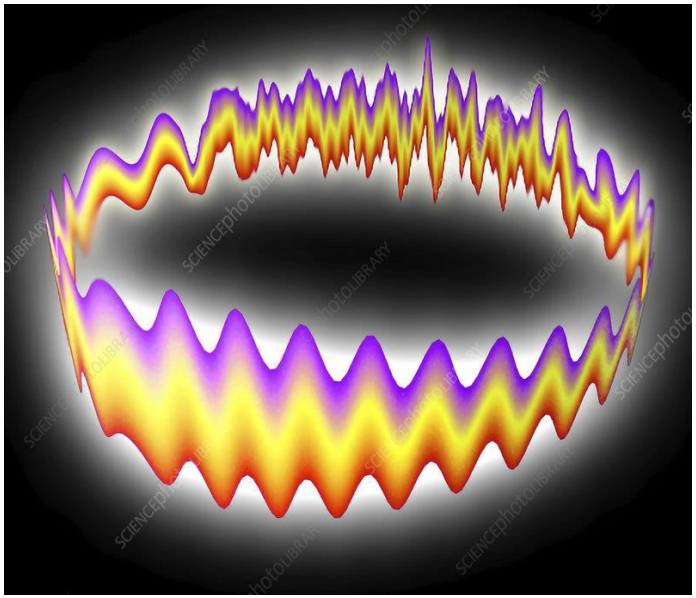
- **A warning or signal before the onset of headache**

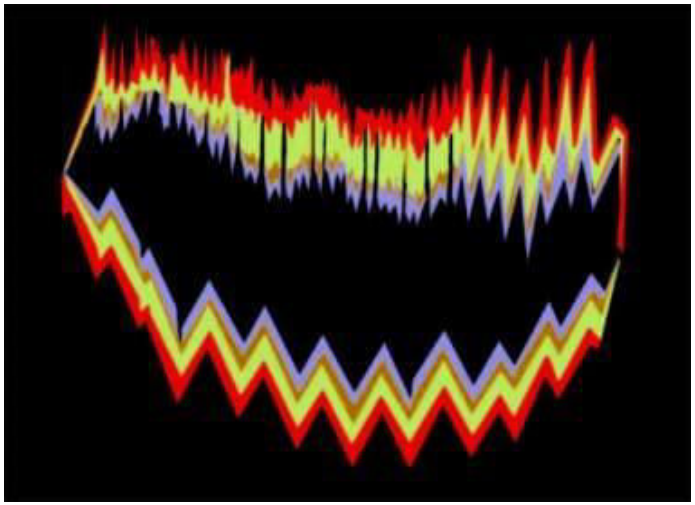
Symptoms

- **Flashing of lights**
- **Zig zag lines**
- **Difficulty in focusing**

Duration 15-30 min

Visual aura

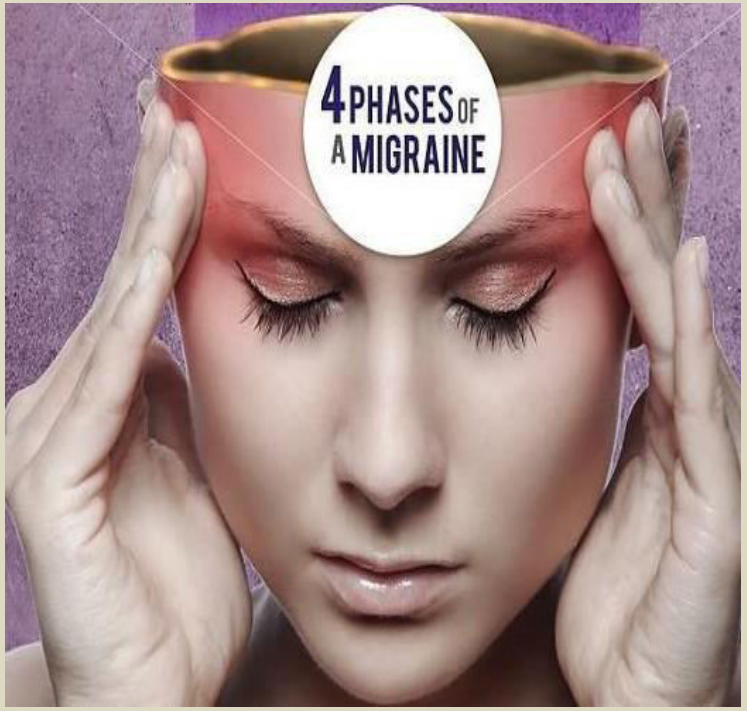




HEADACHE

- Headache is generally unilateral and is associated with ***SYMPTOMS*** like:

- **Anorexia**
- **Nausea**
- **Vomiting**
- **Photophobia**
- **Phonophobia**
- **Tinnitus**



Duration : 4-72hrs

POSTDROME

- **Following headache, patient complains of**

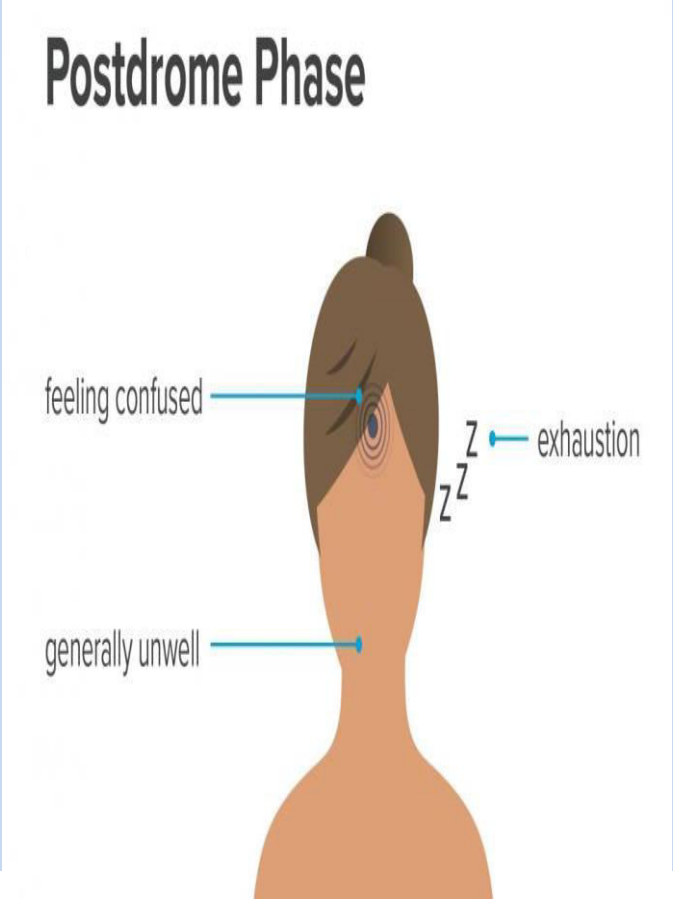
Fatigue

Depression

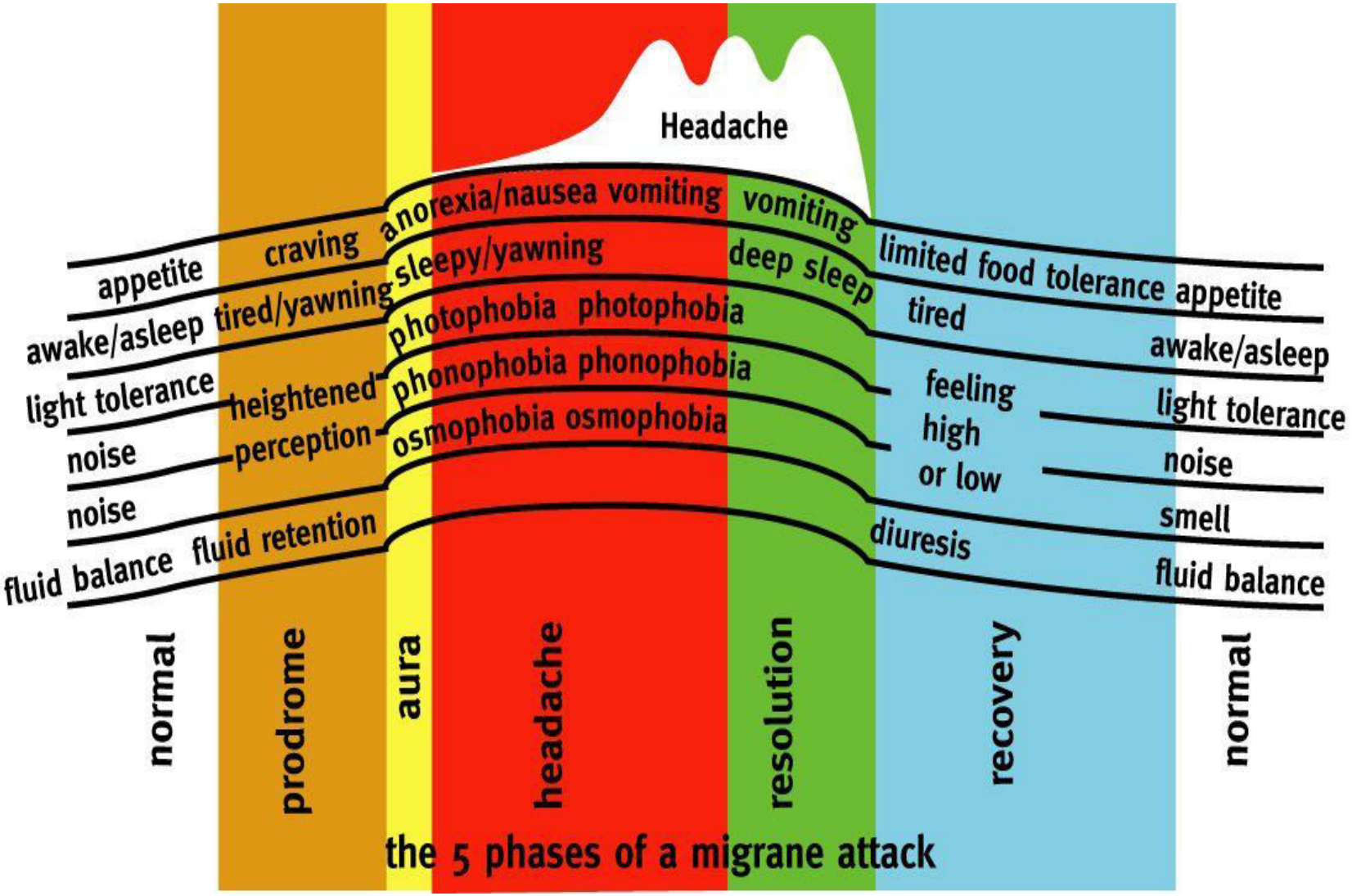
Severe exhaustion

Some patients feel unusually fresh

***Duration*: few hours or up to 2 days**



Summary of phases



CLASSIFICATION

- **According to Headache classification committee of the international Headache society migraine has been classified as:**

- **Common migraine** (without aura)
- **Classic migraine** (with aura)
- **Complicated migraine**

Types of Migraines

Migraine without aura

Headache that comes in stages

May experience nausea, fatigue, irritability, and sensitivity to light and sound

Typically on a localized spot on one side of the head

Migraine with aura

Usually causes visual disturbances for about 30 minutes prior to initial migraine symptoms

May affect speech, taste, or smell

- **Mild** (1/month, upto 8 hr)
- **Moderate** (> 1/ month, intense, 6-24 hr, nausea, vomiting associated)
- **Severe** (2-3/month, severe throbbing, 12-48 hr, vertigo, vomiting associated)

Classical migraine

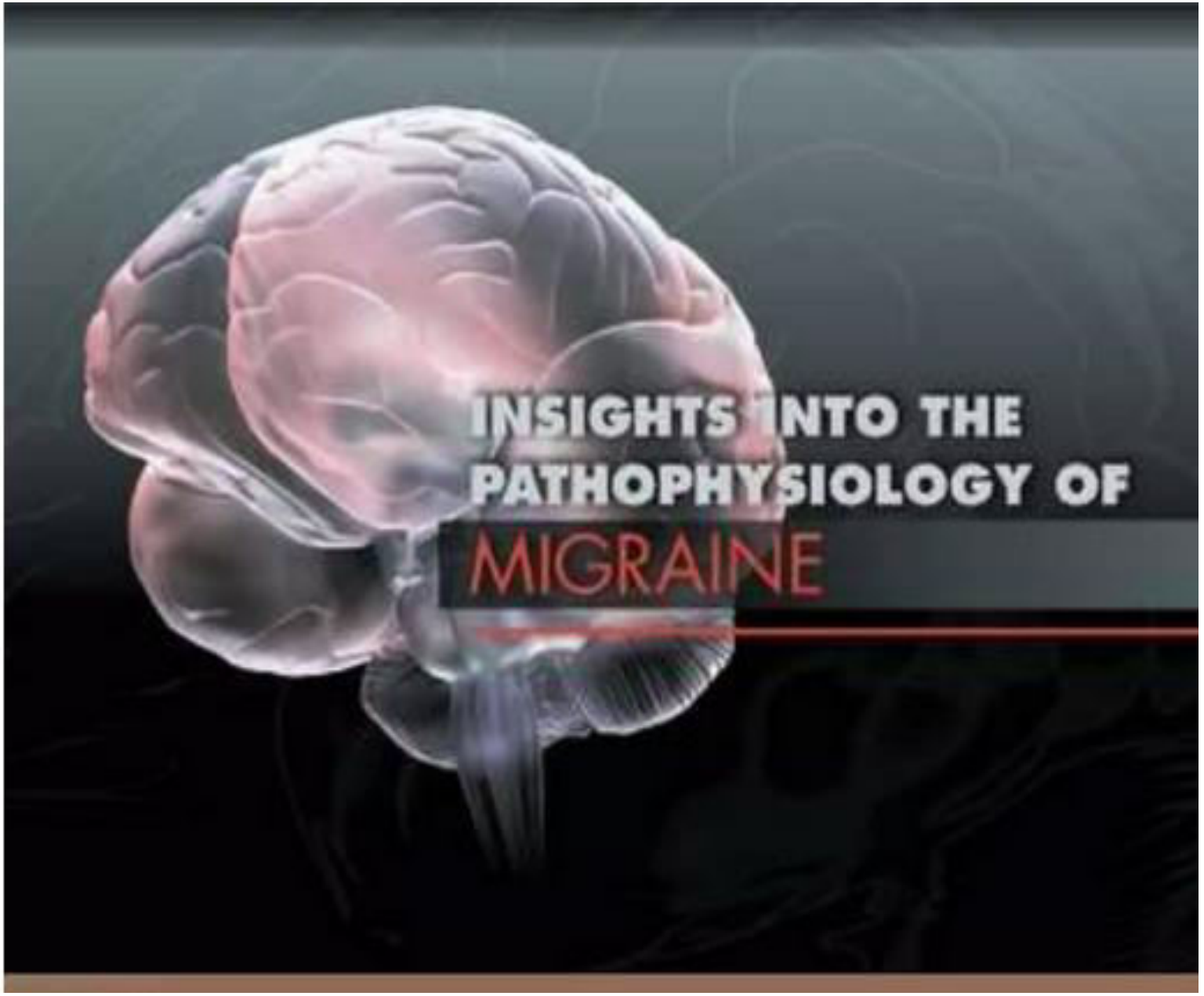
- Migraine with aura (ophthalmic, hemiplegic migraine) is defined as a recurrent disorder involving headache attacks appearing gradually over 5-20 minutes and lasting for less than 60 minutes.
- The aura encompasses focal neurological symptoms that precede or accompany at the onset of migraine attacks.
- **Aura can involve reversible visual and sensory symptoms and speech weakness.**

International Classification of Headache Disorders II. (2004). *Cephalalgia*, Vol.24, Sup.1, pp.1-160

Common migraine

- Migraine without aura (hemicrania simplex, common migraine) is a specific neurological disorder characterized by unilateral, pulsating quality, aggravation on movement, and moderate to severe headache, nausea and photophobia.
- **Most migraineurs suffer from this subtype of migraine, and there are higher frequency and more severe attacks in comparison with migraine with aura.**
- Owing to strong relationship between migraine without aura with menstrual cycle, the menstrual migraine (i.e. pure menstrual migraine and menstrually-related migraine) is categorized in this subtype.

International Classification of Headache Disorders II. (2004). *Cephalalgia*, Vol.24, Sup.1, pp.1-160


INSIGHTS INTO THE
PATHOPHYSIOLOGY OF
MIGRAINE

PATHOPHYSIOLOGY

- **VASCULAR THEORY**

Intracranial/Extracranial blood vessel vasodilation-headache

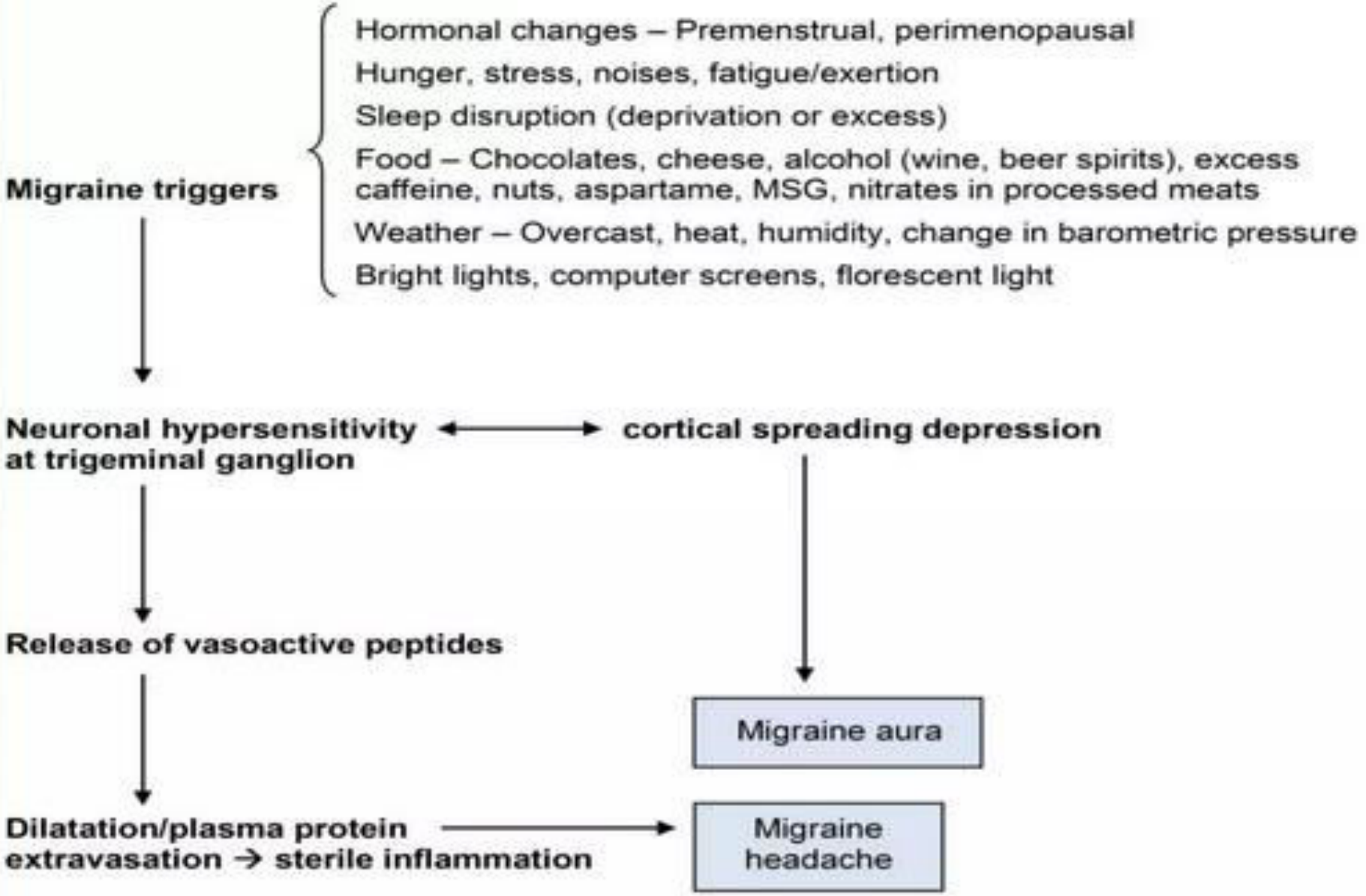
Intracerebral blood vessel vasoconstriction-aura

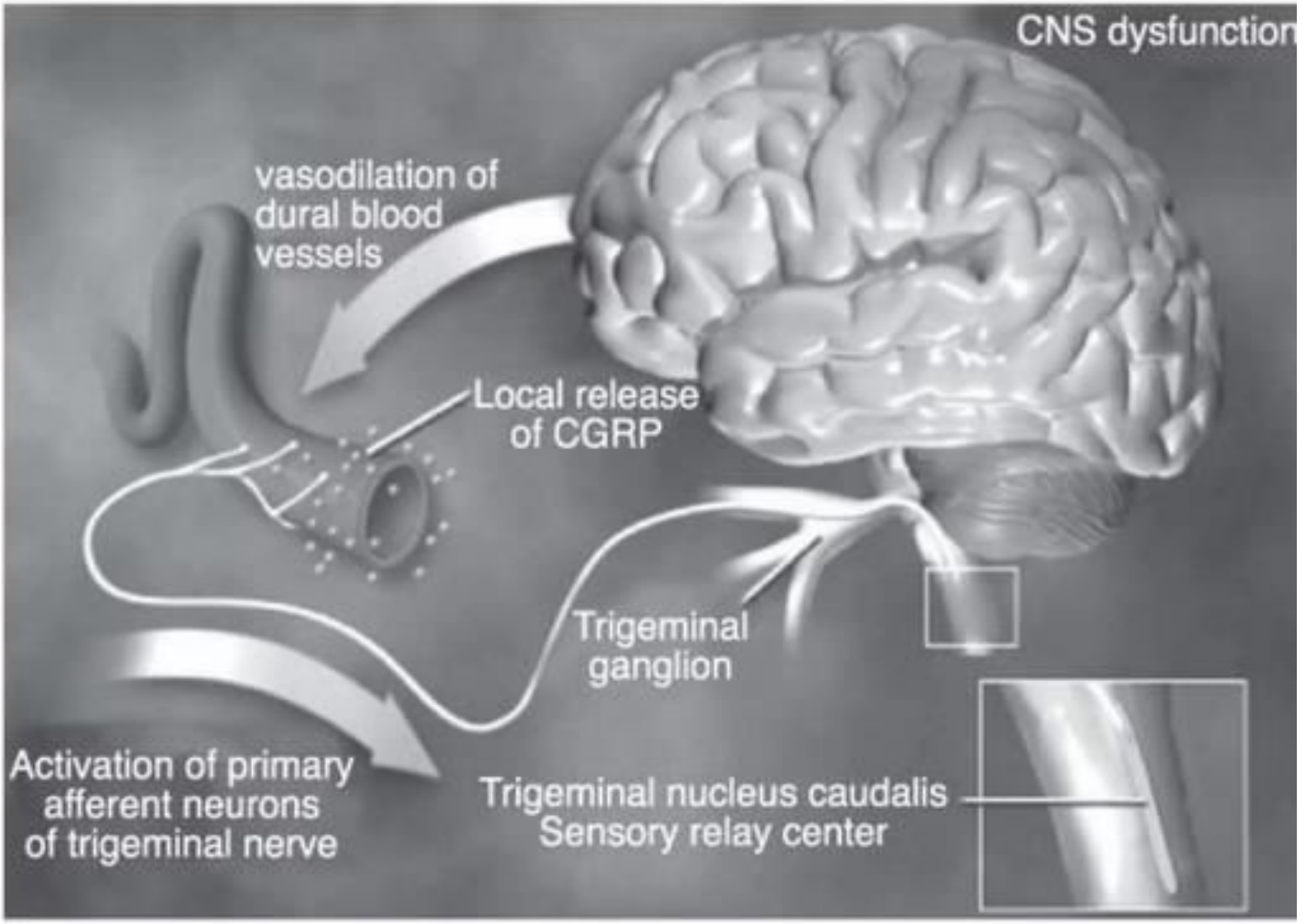
SEROTONIN THEORY

Decrease levels linked to migraine

Specific serotonin receptors found in blood vessels of brain

Migraine pathogenesis



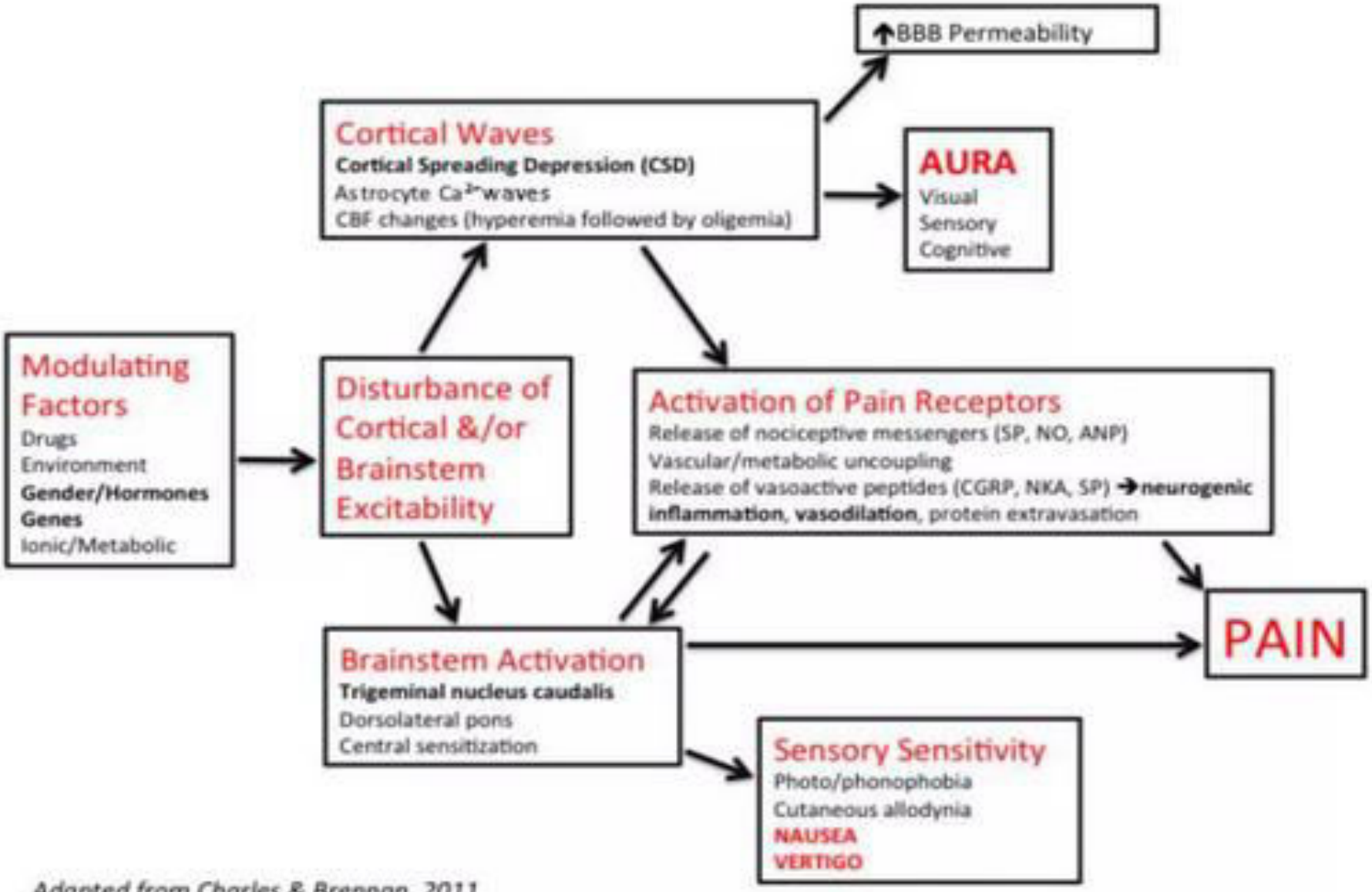

CNS dysfunction
vasodilation of dural blood vessels
Local release of CGRP
Trigeminal ganglion
Activation of primary afferent neurons of trigeminal nerve
Trigeminal nucleus caudalis Sensory relay center

Release of
Neurotransmitter

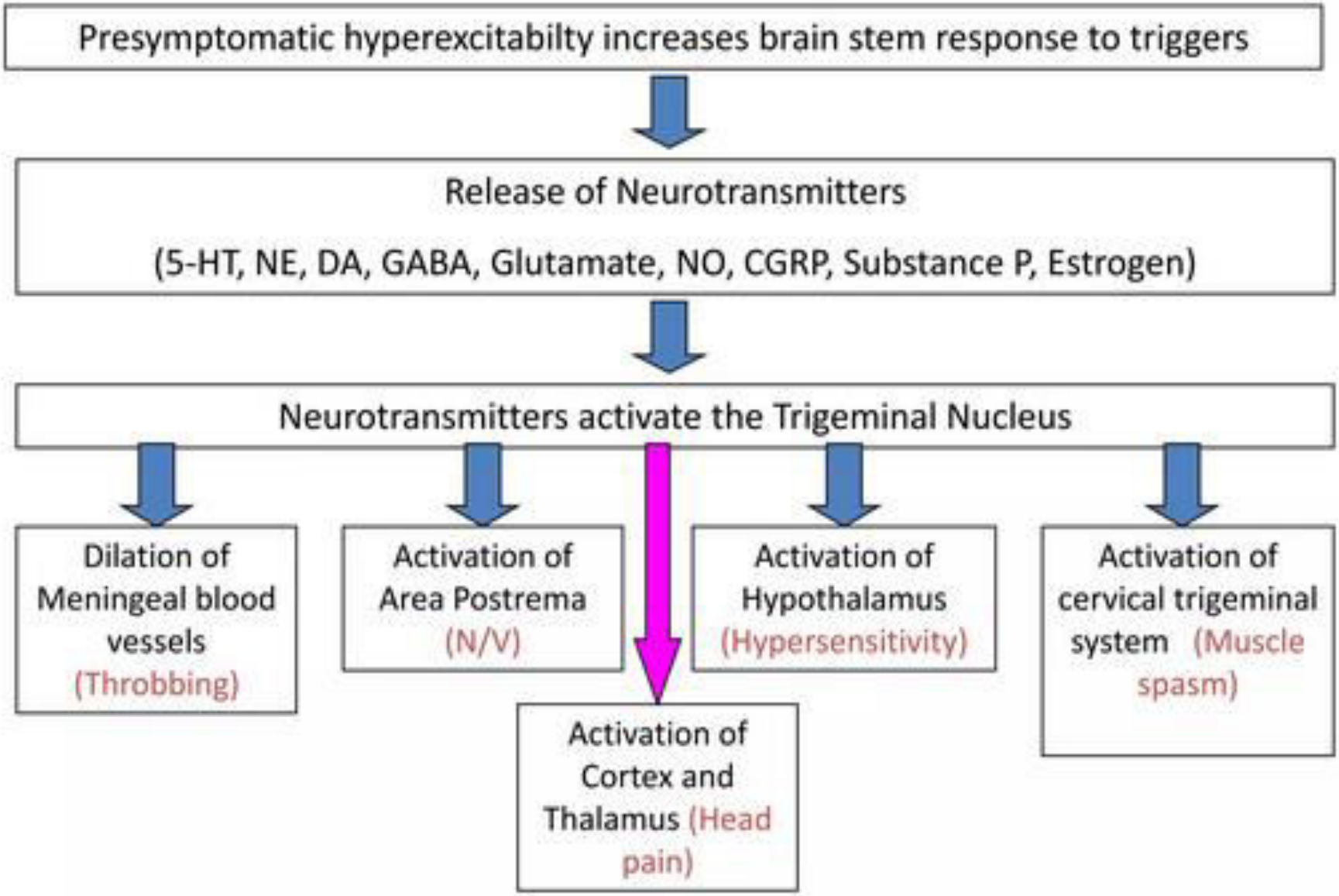
Arterial Activation

Worsening of Pain

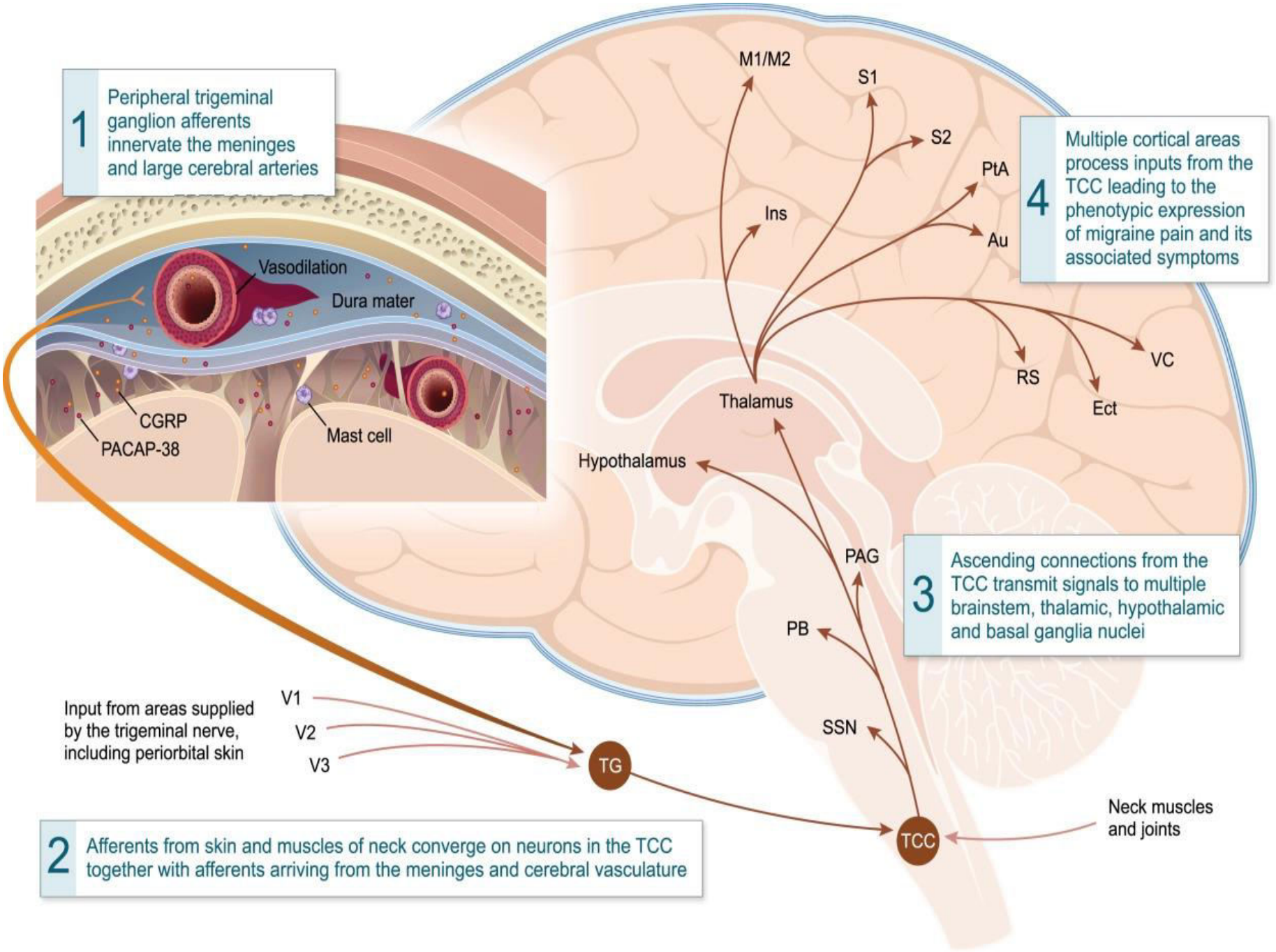
Hypothesized Sequence of Events in Migraine



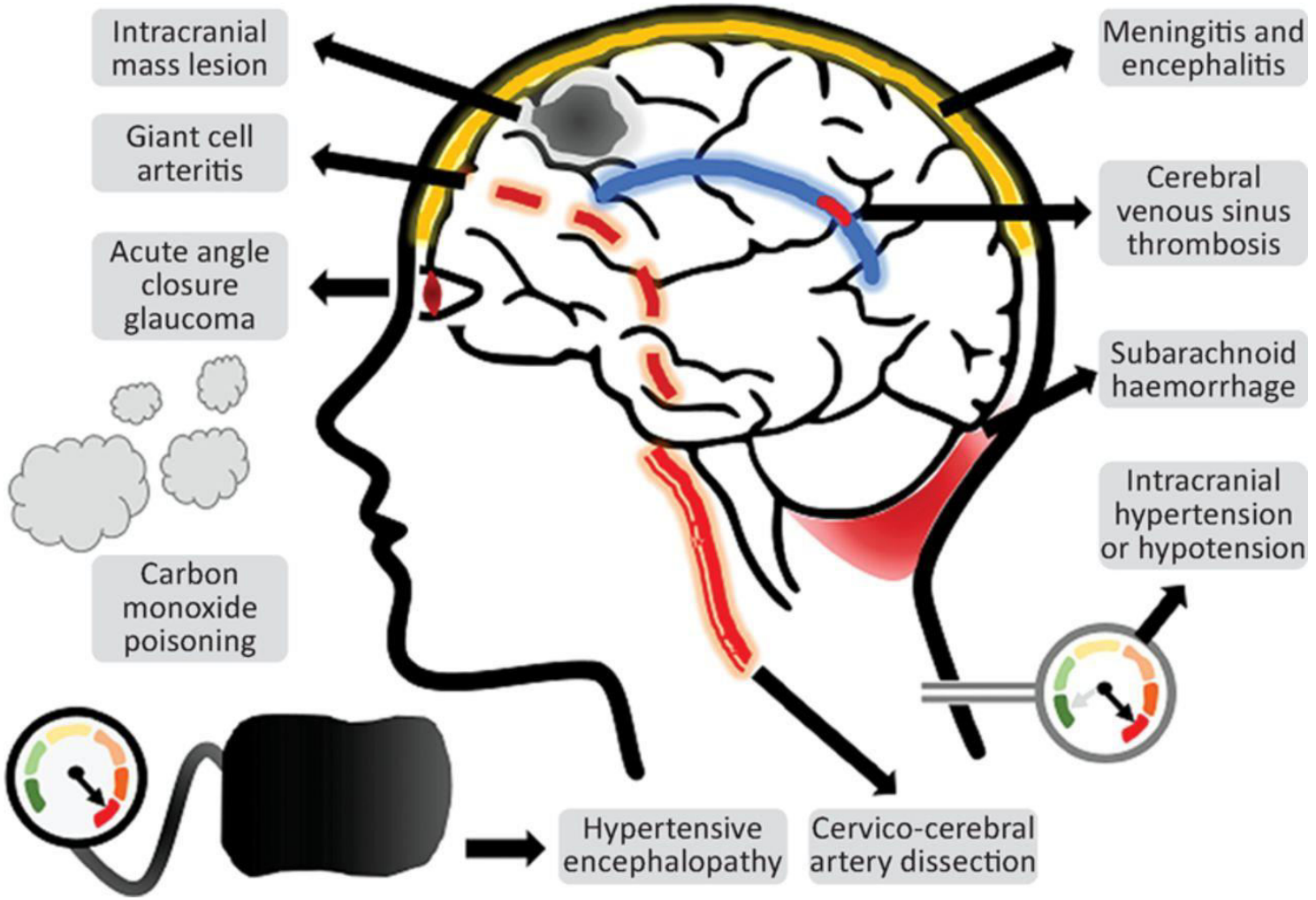
Adapted from Charles & Brennan, 2011



Marcus, DA. *Headache Simplified* 2008.


1
Peripheral trigeminal ganglion afferents innervate the meninges and large cerebral arteries
Vasodilation
Dura mater
CGRP
PACAP-38
Mast cell
M1/M2
S1
S2
PtA
Au
Ins
4
Multiple cortical areas process inputs from the TCC leading to the phenotypic expression of migraine pain and its associated symptoms
VC
RS
Ect
Thalamus
Hypothalamus
PAG
PB
SSN
3
Ascending connections from the TCC transmit signals to multiple brainstem, thalamic, hypothalamic and basal ganglia nuclei
Input from areas supplied by the trigeminal nerve, including periorbital skin
V1
V2
V3
TG
TCC
Neck muscles and joints
2
Afferents from skin and muscles of neck converge on neurons in the TCC together with afferents arriving from the meninges and cerebral vasculature

Differential Diagnosis



Sinus
pain is behind browbone and/or cheekbone.

Cluster
pain is in and around one eye.

Tension
pain is like a band squeezing the head.

Migraine
pain, nausea and visual changes are typical of classic form.

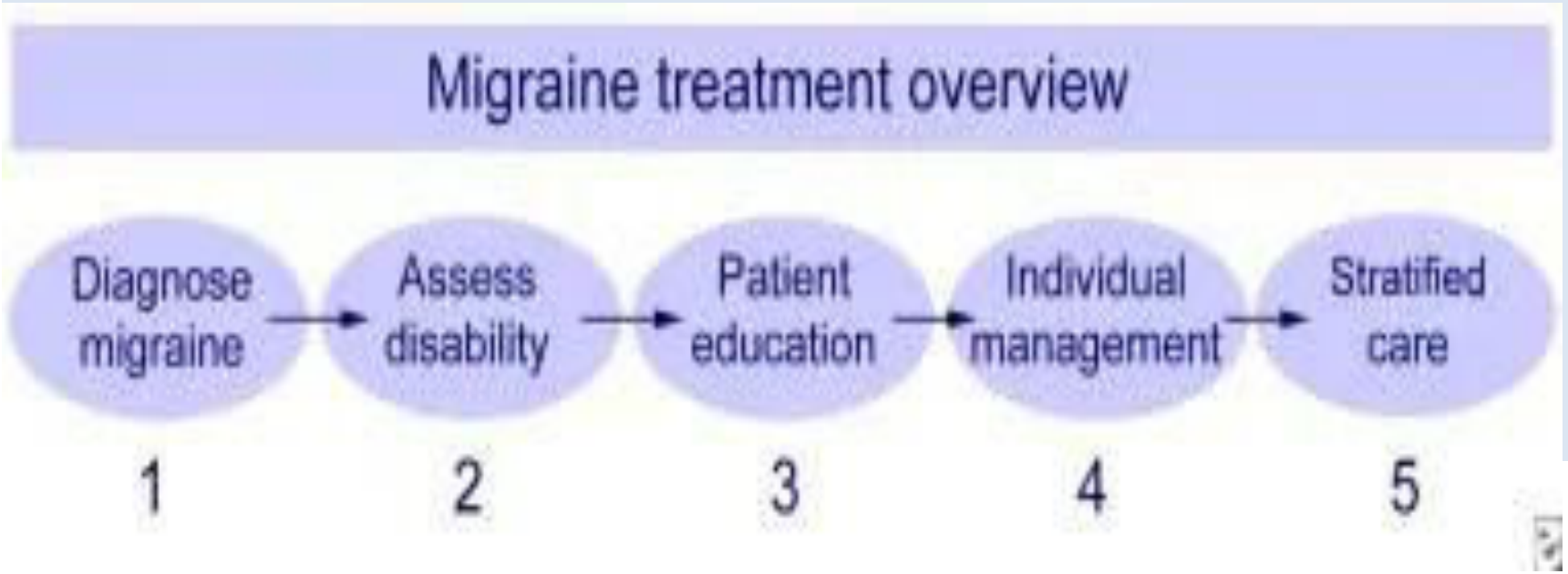
DIAGNOSIS

- **Medical history**
- **Headache history**
- **Migraine triggers**
- **Investigations**

  ECG/ CT Brain/MRI

Management of migraine

- **Not life threatening and not associated with serious illness but can make life miserable**
- **Inherited tendency of cerebral dysfunction and can not be cured completely**
- **Life style modification is important**



GOALS FOR TREATMENT

- Establish diagnosis
- Educate patient
- Discuss findings
- Establish reasonable expectations
- Involve patient in decision
- Encourage patient to avoid triggers
- Choose best treatment
- Create treatment plan

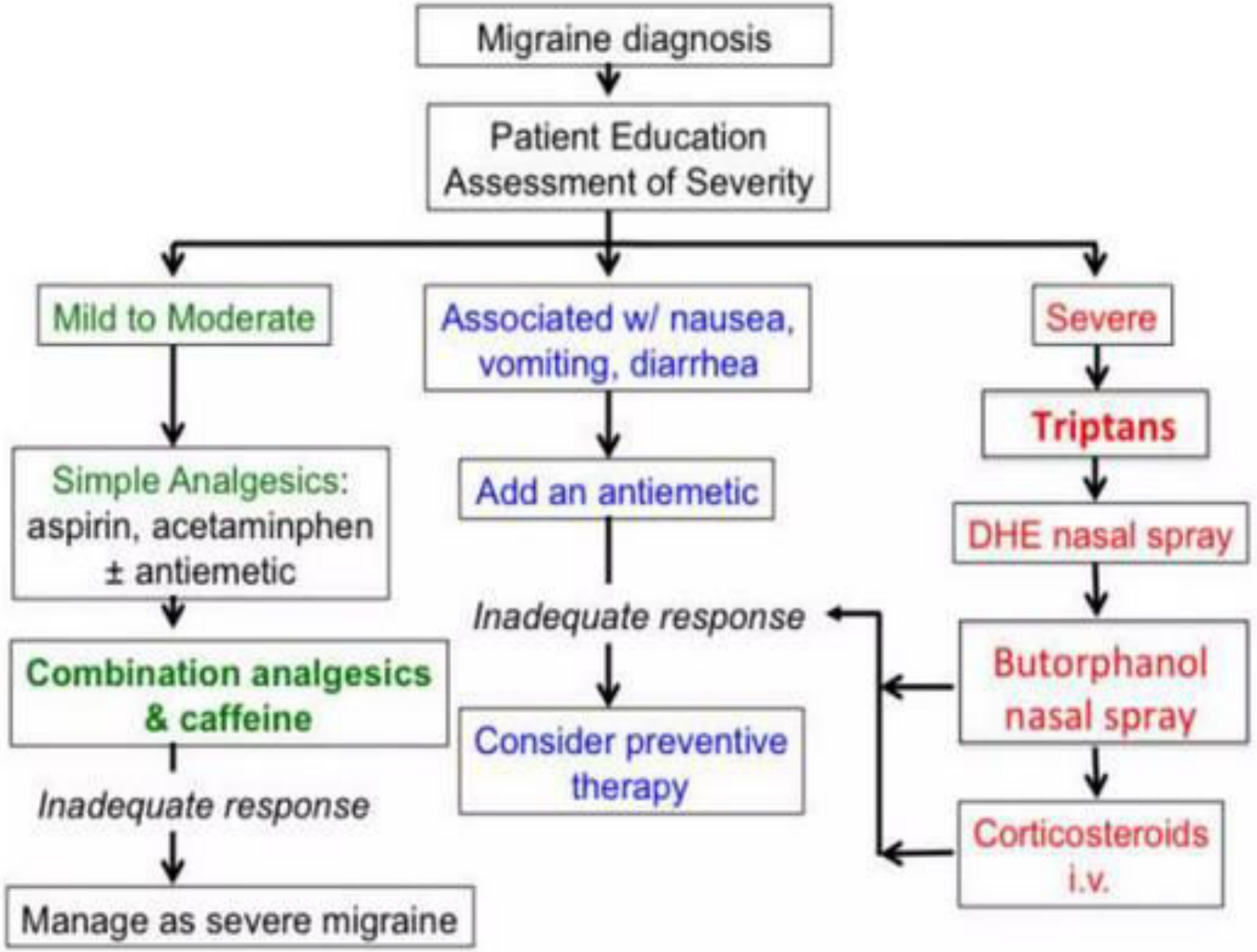
MANAGEMENT

Non-pharmacological treatment

- **Triggers identification**
- **Meditation**
- **Relaxation training**
- **Psychotherapy**

- **Pharmacotherapy**

- **Abortive therapy**
- **Preventive therapy**


Migraine diagnosis
Patient Education
Assessment of Severity
Mild to Moderate
Associated w/ nausea, vomiting, diarrhea
Severe
Simple Analgesics: aspirin, acetaminphen ± antiemetic
Add an antiemetic
Triptans
DHE nasal spray
Inadequate response
Combination analgesics & caffeine
Consider preventive therapy
Butorphanol nasal spray
Inadequate response
Corticosteroids i.v.
Manage as severe migraine
Adapted from Silberstein SD et al., 2000

ABORTIVE THERAPY

- **Non specific treatment**

DRUG	DOSE	ROUTE
Asprin	500-650mg	oral
paracetamol	500mg-4g	oral
Ibuprofen	200-300mg	oral
Diclofenac	50-100mg	Oral/IM
Naproxen	500-750mg	oral

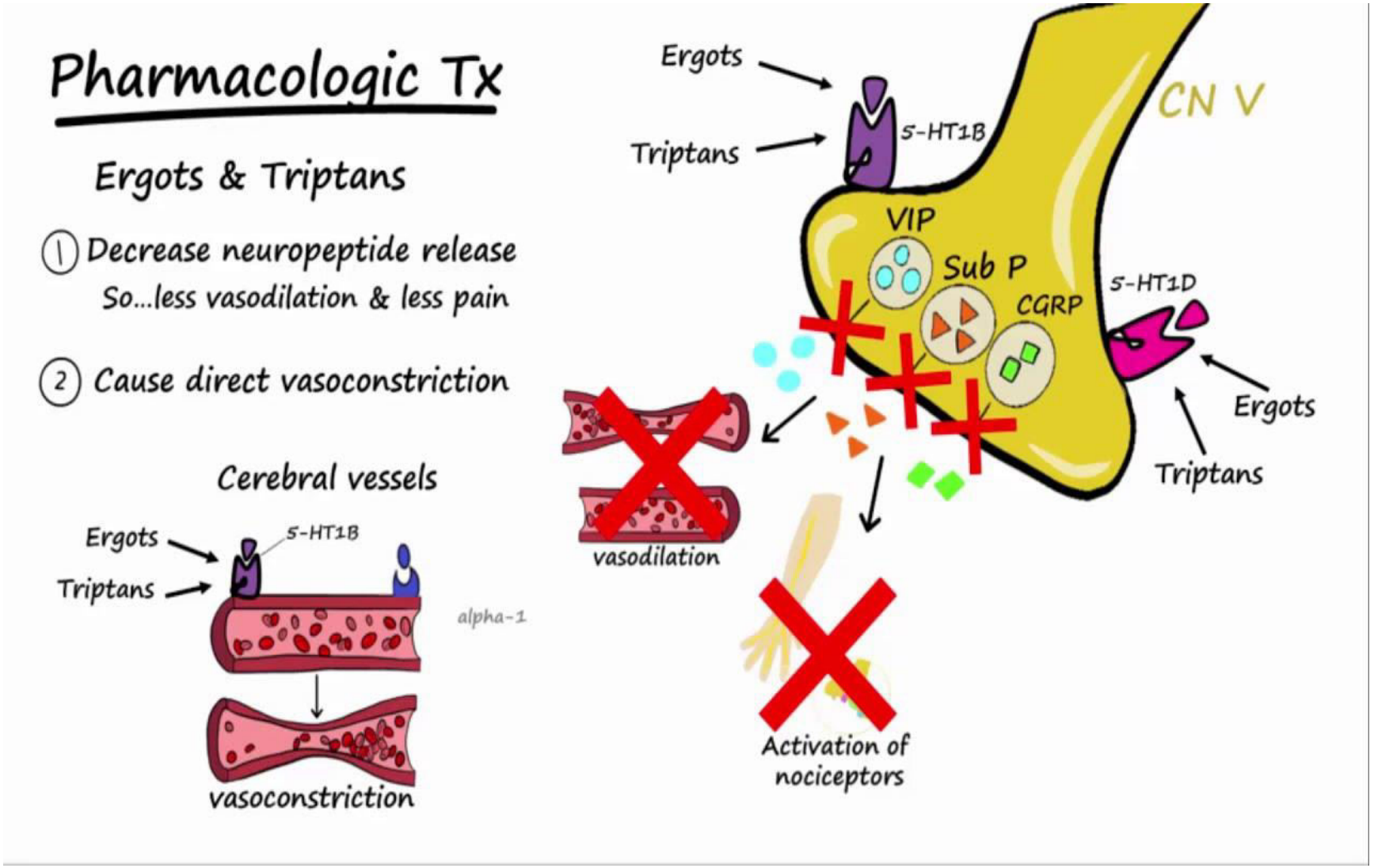
SPECIFIC THERAPY

DRUG	DOSE	ROUTE
ERGOT ALKALOIDS		
Ergotamine	1-2mg/d: max 6g/day	oral
Dihydroergotamine	0.75-1mg	SC
5HTReceptor agonists		
Sumatriptan	25-300mg	oral
	6mg	SC
Rizatriptan	10mg	oral

Ergot Alkaloids

- Ergotamine
  - Mechanism of antimigraine action
    - Exact mechanism unknown
  - Therapeutic uses
    - Drug of choice to stop an ongoing migraine
  - Pharmacokinetics
    - PO, sublingual, rectal, or inhalation
  - Adverse effects
    - Nausea/vomiting, weakness in the legs, myalgia, numbness and tingling in fingers or toes, angina-like pain, tachycardia or bradycardia

Mechanism of action



Acute Treatment - Triptans

- Reasonable first choice for patients with moderate to severe disability from migraines
- Limit use to 2-3 days per week
- Patients who fail one triptan often respond another
- Do not use one triptan within 24 hours of another

Acute Treatment - Triptans

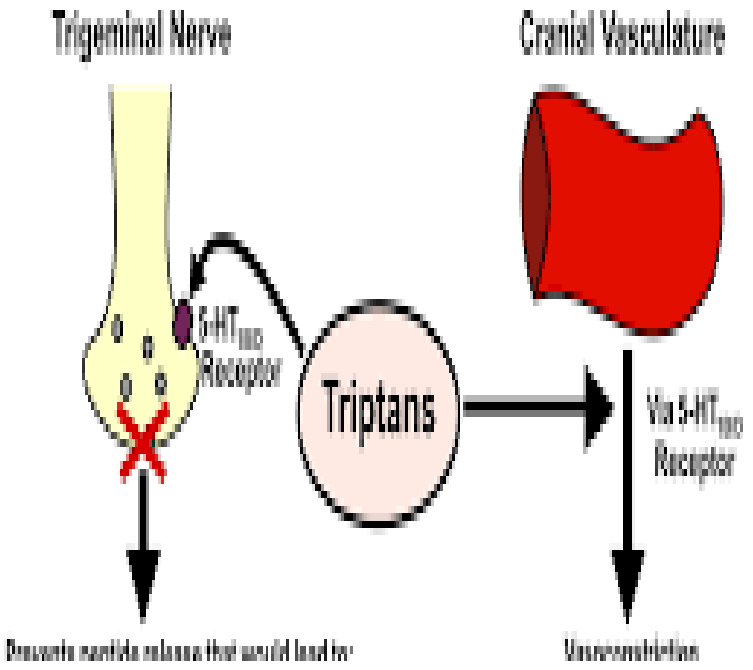
Mechanism of action

- 5HT-1B/1D agonists
- Inhibit release of CGRP & substance P
- Inhibit activation of the trigeminal nerve
- Inhibit vasodilation in the meninges

Precautions

- Ischemic heart dz or stroke
- High risk for CAD
- Pregnancy
- Hemiplegic or basilar migraine
- Ergots
- **Use w/ SSRIs?**

Proposed Triptan Mechanism of Action



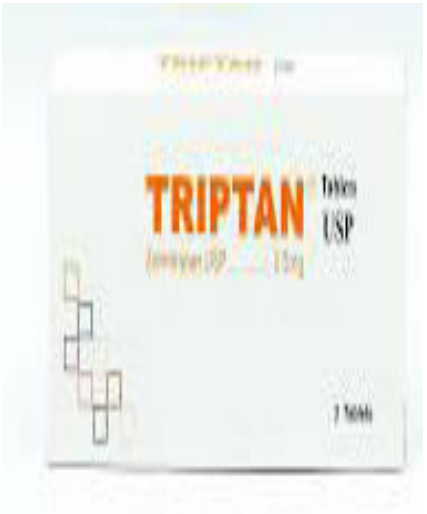
Triptan	First Available	Original Brand Name	Available As					
			T	ODT	NS	SI	BAI	OF
almotriptan	2001	Axert	X					
eletriptan	2002	Relpax	X					
frovatriptan	2001	Frova	X					
rizatriptan	1998	Maxalt, Maxalt-MLT	X	X				X[1]
naratriptan	1998	Amerge	X					
sumatriptan	1992	Imitrex	X		X	X	X	
zolmitriptan	1997	Zomig, Zomig-ZMT	X	X	X			

T=tablet; ODT= orally disintegrating tablet; NS=nasal spray;
BAI=breath activated inhaler; OF=oral film

[1] Under FDA review, but not yet approved as of July, 2017.

Triptan side effects

- Flushing, feeling or warmth
- Chest pressure or heaviness
- Throat tightness
- Paresthesias
- Dizziness, fatigue, drowsiness
- Nausea
- Intolerable taste with nasal formulations



Indications for a preventive agent

- Migraine-related disability ≥ 3d/month
- Migraines last over 48 hours
- Acute treatments are contraindicated, ineffective, or overused
- Migraines cause profound disability or prolonged aura
- Patient preference

General Principles of Preventive Treatment

- Start with a low dose and increase slowly
- Use an adequate trial of 2 to 3 months
- Avoid medication interactions/contraindications
- Monitor with calendar or diary
- Monitor for medication overuse
- Consider comorbid conditions
- Consider preventive medication combinations in refractory patients
- Taper when headaches are controlled

Continuum Lifelong Learning Neurol 2012;18(4):764–782

PREVENTIVE THERAPY

	DRUGS	DOSE (mg/dl)
1	**BETA BLOCKERS**	
	Propranolol	40-320
2	**Calcium channel Blockers**	
	Flunarizine	10-20
	Verapamil	120-240
3	**TCAs**	
	Amitriptyline	10-20
4	**SSRIs**	
	Fluoxetine	20-60

Anti Migraine Drugs

- Prophylactic
  - Beta blockers
  - Valproic acid
  - Topiramate
  - Tricyclic antidepressants
  - Calcium channel blockers (e.g.,verapamil)
  - ACE inhibitors
  - Angiotensin II receptor blockers
  - Methysergide
  - Gabapentin
  - Botulinum toxin A
- Abortive
  - Triptans
  - Ergotamine
  - Dihydroergotamine
  - NSAIDS
  - Isometheptene
  - Tramadol

BETA BLOCKERS

Advantages

- Thoroughly studied and widely used
- Timolol (Blocadren) and propranolol (Inderal) are FDA approved
- Good choice for patients with HTN, CAD, tremor, or anxiety

Adverse effects of Beta Blockers

mnemonic:

BBALD FISH

B bronchoconstriction

B bradycardia

A arrhythmias

L lethargy

D disturbance in glucose metabolism

F fatigue

I insomnia

S sexual dysfunction

H hypotension

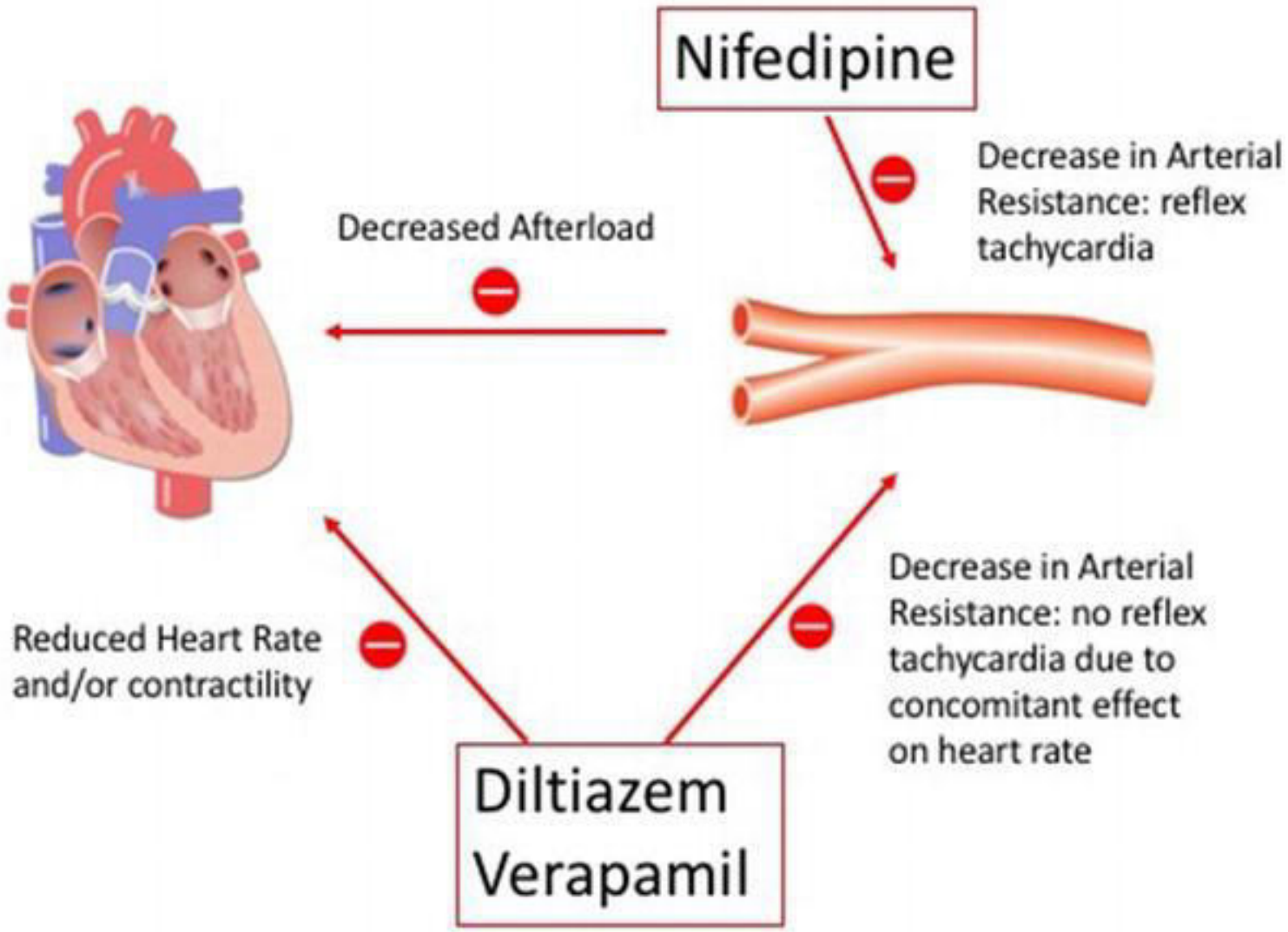
Calcium channel blockers

. Although the mechanism by which calcium channel antagonists affect migraine is not known,

. vasoconstriction , prevention of platelet aggregation and alterations in release and reuptake of serotonin.

. Several trials have indicated some benefit for verapamil and flunarizine In recurrent migraine.

. Verapamil in doses of 80 to 160 mg 3 times a day reduces the incidence of migraine with aura, but it is not as useful in migraine without aura.


Nifedipine
Decrease in Arterial Resistance: reflex tachycardia
Decreased Afterload
Reduced Heart Rate and/or contractility
Decrease in Arterial Resistance: no reflex tachycardia due to concomitant effect on heart rate
Diltiazem
Verapamil

Long term Treatment

- Reducing the attack frequency and severity
- Avoiding escalation of headache medication
- Educating and enabling the patient to manage the disorder
- Improving the patient quality of life

Take home messages/conclusion

- MIGRAINE IS A COMPLEX DISORDER OF BRAIN EXCITABILITY AND NOT SIMPLY A "VASCULAR HEADACHE"
- MIGRAINE IS EXTRAORDINARILY COMMON AND UNDERDIAGNOSED.
- THE MAJORITY OF MIGRAINE PATIENTS CAN BE EFFECTIVELY AND SAFELY TREATED WITH AN ORGANIZED PLAN OF LIFESTYLE MANAGEMENT , ACUTE THERAPY, AND PREVENTIVE THERAPY IF NEEDED
- PROMISING NEW THERAPIES ARE ON THE HORIZON

REFERENCES:

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- Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68:343–9.
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TIME
TO
RELAX